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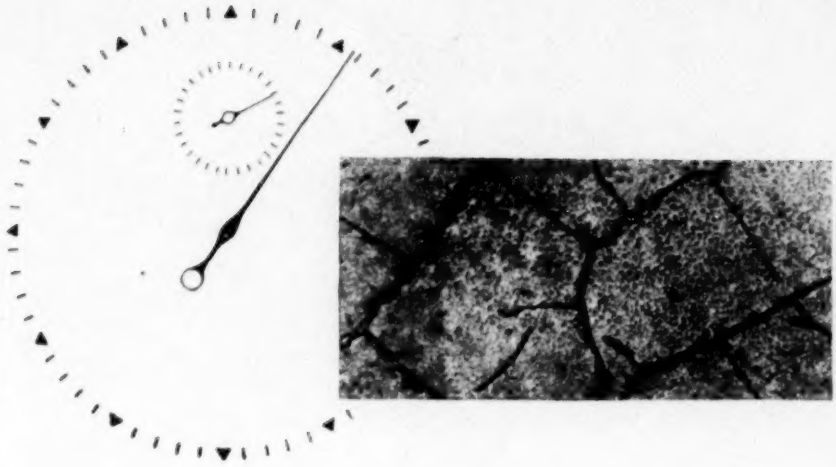

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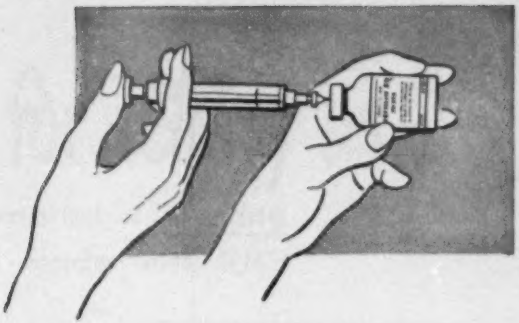

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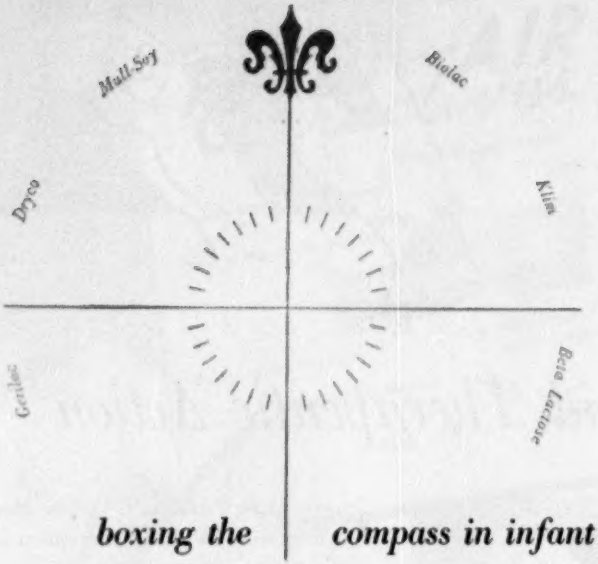

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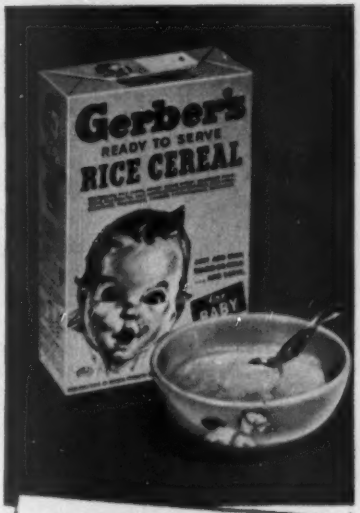

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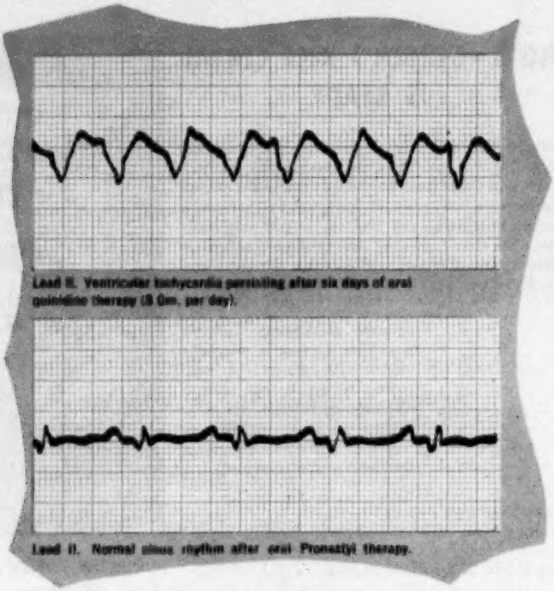

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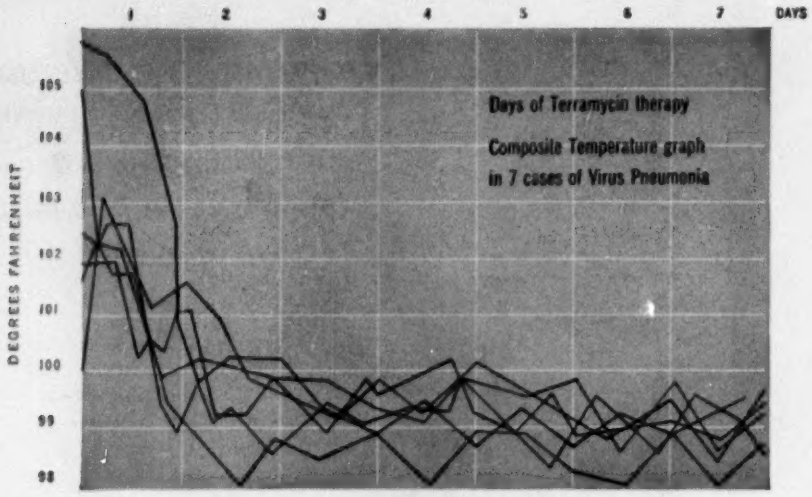

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Melcher, G. W.; Gibson, C. D.; Rose, H. M., and Loveland, Y.: J. A. M. A. 143:1208 (Aug. 12) 1950.

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1. *Blake, F. G.; Frisa, G. J., and Wagner, R. R.: Yale J. Biol. and Med. 22:495 (July) 1950.*
2. *Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950.*

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American Journal of Diseases of Children

VOLUME 80 NOVEMBER 1950 NUMBER 5

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USE OF PHENURONE® IN CONVULSIVE DISORDERS IN CHILDREN

HADDOW M. KEITH, M.D.
ROCHESTER, MINN.

IN RECENT years a number of compounds have been found which are anticonvulsant in action on animals having convulsions induced by electroshock or by substances such as pentylenete (metrazol®) and on patients having convulsive attacks. One such substance is phenacetylurea (phenurone® Abbott; phenacetylcarbamide, Abbott). Everett and Richards showed that this drug suppressed experimentally produced convulsions in mice and that its toxicity when administered to cats and dogs was low. The lethal dose was found to be 3 to 5 Gm. per kilogram of body weight in all species tested.

Gibbs, Everett and Richards [1] have discussed the therapeutic use of phenacetylurea in a group of 90 epileptic patients. Fifty per cent of the patients were maintained free of seizures or were greatly improved, while the remaining 50 per cent were not benefited. The amount of drug used daily for adults was 1.5 Gm. (minimum) to 5.0 Gm. (maximum) given in divided doses. Zeifert [2] later studied 13 cases and found that patients who were refractory to treatment with other anticonvulsants responded well to treatment when phenacetylurea was added to or when it replaced other drugs. He noted that a peculiar psychological regression occurred in a few instances.

Livingston and Kajdi [3] reported their experiences with the drug in the treatment of 104 patients, 73 of whom had idiopathic and 31 organic (secondary) epilepsy.[3] Seventy-one of their patients were less than 15 years of age. In 45 patients the attacks were controlled or nearly so, and in 53 the drug was of no benefit. In 27 per cent of the patients untoward reactions developed, the most distressing being personality changes. Rash occurred in two patients and hepatitis in one patient.

From the Section on Pediatrics, Mayo Clinic.

1. Gibbs, F. A.; Everett, G. M., and Richards, R. K.: Phenurone in Epilepsy, Dis. Nerv. System **10**:47-49 (Feb.) 1949.

2. Zeifert, M.: Phenurone in Epilepsy, Dis. Nerv. System **10**:245-248 (Aug.) 1949.

3. Livingston, S., and Kajdi, L.: The Use of Phenurone in the Treatment of Epilepsy, J. Pediat. **36**:159-165 (Feb.) 1950.

Carter and Merritt [4] evaluated phenacetylurea administration in 60 patients. They noted toxic reaction in 27 patients including two with jaundice and two with morbilliform rash.

In the past 20 months my colleagues and I have treated with phenacetylurea [5] 35 patients (34 children, 1 adult) who had convulsive disorders and who have been observed for periods varying from three to 20 months, as well as one patient who has been under observation for two months and whose attacks have ceased. All these patients had been treated with other drugs, singly or in combination and in varying amounts. This is not to say that these other drugs were always administered in amounts which might be considered satisfactory (to the point of controlling attacks or until evidence of toxic reaction appeared). However, the phenacetylurea was given because the attacks were not otherwise controlled.

It is advisable in reporting the results of treatment of recurring convulsions to have had prolonged periods of observation. However, since all these patients had been treated by other methods, without satisfactory outcome, and since many of them were greatly benefited by the phenacetylurea, it was felt to be worth while to make a preliminary report. In accordance with common practice, the patients have been divided into three groups. The first group consists of those patients who during the period of treatment have had no "attacks" of any type. These are designated as "well" (not "cured"). They correspond to the patients reported as "controlled" by Livingston and Kajdi.[3] The second group consists of those patients whose attacks have become less frequent or less severe or both but who continue to have recognizable "attacks." These are designated as "improved." The third group consists of those patients who have not been benefited to any extent by the treatment. Our results are judged on the basis of control of the attacks (grand or petit mal or equivalents). Some of our patients are retarded mentally, and, while we do not expect to improve their mental status, we consider the control of their attacks as definite improvement.

Of the 35 patients observed for the three months or more, eight (23 per cent) have been entirely free from attacks for periods of three to 17 months. Fifteen patients (43 per cent) have been improved, and 12 have not been benefited. Thus 23 patients have had a decided reduction in the number of attacks or have been entirely free from convulsions while taking phenacetylurea (table 1).

Four of the 36 patients had a morbilliform rash shortly after they began to take the drug. Two of the four stopped taking the phenacetylurea for a short time, then resumed its use without a recurrence of

4. Carter, S., and Merritt, H. H.: Medical Therapy of Epilepsy, Journal-Lancet **70**:103-106 (March) 1950.

5. The phenacetylurea was supplied by Abbott Laboratories, North Chicago, Ill.

TABLE 1.—*Results of Treatment with Phenacetylurea*

Results	Patients	
	Number	Per Cent*
Total number	36	..
Well (no known attacks)	8	23
Improved	15	43
Not benefited	12	34
Observed less than 3 months	1	..

* Per cent of the 35 patients who have been observed for three months or more.

TABLE 2.—*Blood Counts Before and After Administration of Phenacetylurea*

Case	Administration of Phenacetylurea		Hemoglobin, Gm.	Red Blood Cells, Millions	White Blood Cells
	Total Gm.	Days			
1	382.5	365	12.4	....	5,700
			15.9	4.93	9,200
2	450	300	12.2	....	7,100
			13.7	....	9,400
3	90	90	11.4	3.79	4,200
			11.4	....	6,700
4	180	120	....	4.85	6,400
			12.8	5.08	5,800
5	270	180	11.7	....	3,900
			14.0	4.90	6,550
6	90	60	12.4	4.50	5,600
			....	....	7,000
7	300	120	13.0	4.72	5,600
			....	....	7,200
8	28.5	25	13.2	....	5,100
			(86%)	4.30	9,700
9	720	365	12.2	4.51	7,300
			12.1	....	7,100
10	90	90	12.7	4.48	5,300
			....	....	6,700
11	315	365	12.4	4.37	6,600
			10.9	....	3,700
12	600	120	12.4	....	4,700
			11.8	3.72	4,600

TABLE 3.—*Liver Function Tests After Administration of Phenacetylurea*

Cases	Administration of Phenacetylurea		Serum Bilirubin, Units		Sulfobromophthalein Sodium Retention, Grade
	Total Gm.	Days	Direct	Indirect	
1	330	270	0	0.5	0
4	180	120	1.3	0.3	3*
6	63	42	0	0.7	0
11	330	330	0	0.5	0
12	1,071	257	0	0.3	0
13	195	130	...	...	1

* This patient died of abdominal carcinomatosis.

TABLE 4.—*Data on Patients Who Received Phenacetylurea*

Case	Age, Years	Diagnosis	Electroencephalogram	Intelligence Quotient	Previous Medication	Phenacetylurea		Result	Complications
						Gm.	Times a Day		
1	8	Grand mal; mental retardation; psychomotor seizures; schizophrenia	Dysrhythmia	86 (1948); 63 (1949)	Mephobarbital; diphenylhydantoin sodium	0.5	3	No convulsions, 13 months	.....
2	10	Grand mal; petit mal	Dysrhythmia; petit mal	..	Ketogenic diet	0.5	4	No attacks, 3½ months	.....
3	6	Grand mal; petit mal	Dysrhythmia; petit mal	..	Mephobarbital; phenobarbital; trimethadione; ketogenic diet; methylphenylethyl hydantoin	1.0	1	No attacks, 15 months	.....
4	7	Grand mal; brain tumor	Dysrhythmia	..	Trimethadione	0.3	3	No attacks, 1 year	Mild rash
5	12	Petit mal; behavior problem	Dysrhythmia, left temporal region	86	Phenobarbital; diphenylhydantoin sodium	0.5	3	No attacks, 7 months	.....
6	3½	Petit mal	Dysrhythmia with excessive hyperventilation	..	Diphenylhydantoin sodium	0.5	2	No attacks, 10 months	.....
7	14	Petit mal; grand mal; congenital syphilis	Dysrhythmia	..	Phenobarbital; trimethadione	0.3	4	No attacks, 20 months	.....
8	8	Convulsive disorder; mental retardation	Dysrhythmia; petit mal	..	Diphenylhydantoin sodium; trimethadione	0.3	3	No attacks, 3 months	.....
9	26	Grand mal; petit mal	Dysrhythmia	..	Bromides; trimethadione; methylphenylethyl hydantoin	0.3	3	Improved; "much help"	Nausea; vomiting; rash
10	13	Petit mal	Dysrhythmia; petit mal	70	Diphenylhydantoin sodium; trimethadione	0.5	4	Grand mal improved; few petit mal seizures persist	.....
11	6	Grand mal; petit mal	Left occipital delta activity	..	Bromides; phenobarbital; diphenylhydantoin sodium	0.5	2	Much improved	.....
12	10	Grand mal; petit mal	Dysrhythmia; petit mal	..	Mephobarbital; trimethadione; phenobarbital; diphenylhydantoin sodium; methylphenylethyl hydantoin; paramethadione	0.5	2	Improved	Rash 4 days; recurrence of rash later
13	8	Grand mal	Dysrhythmia	..	Mephobarbital; phenobarbital; ketogenic diet	0.5	4	Much improved, 8 months	.....
14	9	Grand mal; mental retardation; cerebral agenesis	Bitemporal delta activity	36	Diphenylhydantoin sodium	0.25	3	Temporary improvement, 6 weeks	.....
15	1	Convulsive disorder	Dysrhythmia	..	Phenobarbital	0.25	3	Improved, 14 months	.....
16	17	Grand mal; petit mal	Generalized delta activity	116	Trimethadione; diphenylhydantoin sodium	0.5	4	Improved; 1 attack, 9 months	.....
17	5	Petit mal	.....	..	Mephobarbital; diphenylhydantoin sodium; paramethadione; methylphenylethyl hydantoin	0.5	5 or 6	Improved, 14 months	.....
18	4	Convulsive disorder; cerebral palsy	Dysrhythmia	64	Trimethadione; phenobarbital; diphenylhydantoin sodium; methylphenylethyl hydantoin	0.5	4	Most effective medicine used	.....
19	11	Grand mal; petit mal	Dysrhythmia; petit mal	..	Trimethadione; phenobarbital	0.5	3	Improved*	.....
20	12	Psychomotor seizure	Delta activity	68	Trimethadione; phenobarbital; diphenylhydantoin sodium; methylphenylethyl hydantoin	0.5	2	Improved	.....

TABLE 4.—*Data on Patients Who Received Phenacetylurea (Continued)*

Case	Age, Years	Diagnosis	Electroencephalogram	Intelligence Quotient	Previous Medication	Phenacetylurea: Gm.	Phenacetylurea: Times a Day	Result	Complications
21	2	Convulsions; cerebral defect	Dysrhythmia	..	Mephobarbital; trimethadione; phenobarbital; diphenylhydantoin sodium; methylphenylethyl hydantoin; glycerin	0.25	3	Improved, 3 months	.....
22	12	Convulsions; mental retardation	Generalized high potential dysrhythmia	36	Phenobarbital; mephobarbital; diphenylhydantoin sodium; paramethadione; ketogenic diet	0.5	4	Much improved, 8 months	.....
23	16	Convulsions; grand mal	Dysrhythmia	91 (1946); 79 (1949)	Phenobarbital; diphenylhydantoin sodium; mephobarbital; trimethadione	0.5	5 or 6	Much improved, 17 months	.....
24†	14	Grand mal; petit mal	Dysrhythmia; petit mal	87	Phenobarbital; diphenylhydantoin sodium; trimethadione; methylphenylethyl hydantoin; glutamic acid	0.5	6	Improved	Rash first few days; liver dysfunction
25	14	Grand mal; petit mal; nephrosis; nephritis	Dysrhythmia; petit mal	42	Phenobarbital; trimethadione; methylphenylethyl hydantoin; amphetamine sulfate; glutamic acid	0.5	6	Few grand mal convulsions; petit mal	.....
26	1	Convulsions; mental retardation	Dysrhythmia	..	Trimethadione; phenobarbital	0.5	2	Doubtful benefit	.....
27	2	Convulsions	"Negative"	..	Phenobarbital; diphenylhydantoin sodium; mephobarbital	0.5	3	No benefit, 1 month	.....
28	13	Grand mal	Dysrhythmia	98	Diphenylhydantoin sodium	0.5	4	No benefit, 3 months	.....
29	14	Petit mal	Dysrhythmia; petit mal	..	Phenobarbital; trimethadione; ketogenic diet	0.5	3	No benefit, 5 months	.....
30	6	Convulsions; mental retardation	Dysrhythmia, grade 2	76	Phenobarbital; diphenylhydantoin sodium; mephobarbital; trimethadione	0.25	3	No benefit, 5 months	.....
31	14	Convulsions	Dysrhythmia; petit mal	..	Phenobarbital; trimethadione; diphenylhydantoin sodium; paramethadione	0.5	4 or 5	No benefit, 4 months	.....
32	7	Grand mal; petit mal	Dysrhythmia	..	Phenobarbital; diphenylhydantoin sodium; mephobarbital; trimethadione	0.5	2	No benefit, 3 weeks	.....
33	2	Petit mal	Dysrhythmia; petit mal	..	Phenobarbital; diphenylhydantoin sodium; trimethadione	0.5	5	No benefit, 2 months	.....
34	11	Convulsions	Dysrhythmia	..	Phenobarbital; diphenylhydantoin sodium	0.5	3	No benefit, 1 month	.....
35	3	Grand mal	Dysrhythmia	..	Phenobarbital; diphenylhydantoin sodium; trimethadione; ketogenic diet; glycerin	0.5	2	Doubtful benefit, 2 months	.....
36	11	Photic; grand mal; petit mal	Dysrhythmia	..	Trimethadione; phenobarbital; diphenylhydantoin sodium; amobarbital sodium; mephobarbital	0.5	4	No benefit, 3 weeks	.....

* This patient was observed only two months.
† The patient died of abdominal carcinomatosis.

the rash. The remaining two patients attempted to continue taking the drug, as it controlled their attacks, but they were forced to discontinue its use because of the repeated recurrence of the rash accompanied with generalized itching.

In 12 patients we were able to obtain repeated leukocyte counts. In others the counts were made elsewhere and considered satisfactory but not reported to us. In none of the 12 cases was there leukopenia (table 2).

We were able to perform serum bilirubin and sulfobromophthalein sodium retention tests in 6 patients after the administration of amounts of phenacetylurea varying from 63 to 1,071 Gm. (table 3). Five of these patients showed normal serum bilirubin and no significant amount of sulfobromophthalein sodium retention. One patient had serum bilirubin levels of 1.3 mg. per 100 cc. (direct) and 0.3 mg. (indirect) and a grade 3 retention of the dye. At the time, however, she was suffering from generalized abdominal carcinomatosis, secondary to an ovarian tumor (demonstrated at operation). Since the liver was involved, this may well have been the cause of the dye retention. (Necropsy was not permitted.)

One patient was reported to us as being entirely free from convulsions but that "phenurone caused a mental defect." Our original diagnosis had been retarded mental development with psychomotor epilepsy. He was subsequently studied at the Emma Pendleton Bradley Home, and a diagnosis of schizophrenia was entertained. Dr. M. W. Laufer reported after considerable study that this patient's behavior difficulty was not due to phenacetylurea.

One other patient (not included in this series) was reported to us as having an unfavorable personality disturbance. We have not had the opportunity to follow this patient personally.

Table 4 summarizes the data in regard to the 36 patients.

SUMMARY

The observations here reported confirm the reports of other workers that phenacetylurea is a useful addition to the therapeutic agents that are used in treating epileptic patients. It may successfully control attacks in some patients whose convulsions have not been controlled by other forms of treatment, even when a gross neurological defect may be present. It may be used in combination with other anticonvulsants. In common with most drugs, however, it may produce unfavorable side reactions, mainly dermatitis medicamentosa, unfavorable personality disturbance and, in rare cases, disturbance of liver function. When used with suitable precautions, it appears to be a useful addition to the list of anticonvulsant drugs.

TUBERCULOSIS IN CHILDREN

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THIS article is a review of the cases of 100 consecutive admissions during 1949 (from January 14 to August 29) to the children's division of Sea View Hospital. An attempt is made to correlate the findings on admission and those during at least an eight month period following admission. Several of the practical problems of tuberculosis in children are amplified.

The purpose of this article is to present to the pediatrician the picture of tuberculosis as it is seen in the wards of a large tuberculosis hospital for children. Our impression is that the pediatrician, who has little contact with a tuberculosis hospital, is not sufficiently aware of this picture and is handicapped when confronted with tuberculosis in his practice.

In the table are given the diagnoses made at Sea View Hospital, and they are submitted at this point for orientation. Roentgenologic examination was the chief aid in the diagnoses.

Primary pulmonary tuberculosis is subdivided into the primary complex, miliary and progressive primary types. The arrows in the table indicate that the miliary and progressive primary disease have "passed through" the primary complex stage. The primary complex is further subdivided into cases with (1) both tracheobronchial glandular and parenchymal components (demonstrable by roentgenograms); (2) tracheobronchial component only (demonstrable by roentgenograms), and (3) parenchymal component only (demonstrable by roentgenogram).

In one of the two with miliary tuberculosis a primary complex (with a tracheobronchial glandular and a parenchymal component) was also observed, but it was not seen in the other patient. The patient with progressive primary tuberculosis was a 9 month old white girl in whom roentgenograms showed consolidation in the upper lobe of the left lung.

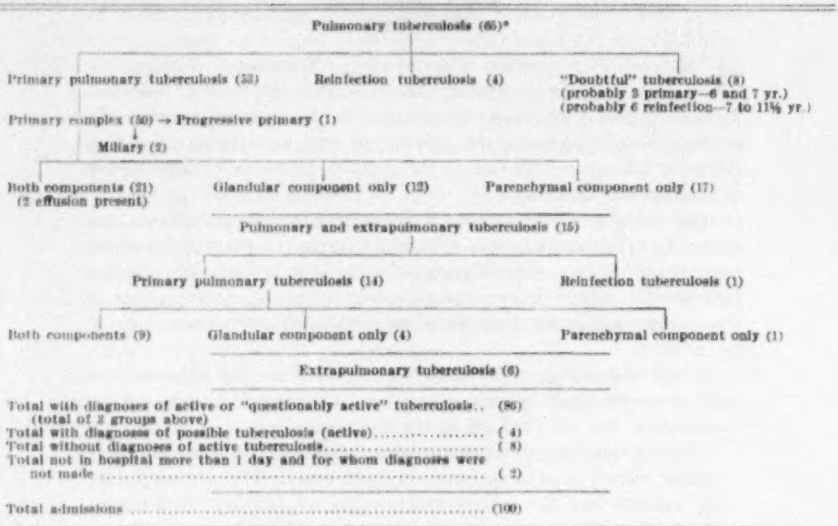
From the Pediatric Service of Sea View Hospital, Staten Island, N. Y., Bret Ratner, M.D., Director.

with several suspicious cavities, and a 4 cm. cavity in the dorsal segment of the lower lobe of the left lung.

Four patients with definite reinfection tuberculosis were observed. The age range of the patients was from 9 to 13 years. All had either moderately or far advanced tuberculosis.

Eight patients with pulmonary tuberculosis, the classification of which into primary or reinfection tuberculosis was difficult, were observed. Two are believed to have primary tuberculosis (with the parenchymal component of a primary complex). All eight patients had

Summary of Admission Diagnoses


Pulmonary tuberculosis (65)*
Primary pulmonary tuberculosis (53)
Reinfection tuberculosis (4)
"Doubtful" tuberculosis (8)
(probably 2 primary—6 and 7 yr.)
(probably 6 reinfection—7 to 11½ yr.)
Primary complex (50) → Progressive primary (1)
Miliary (2)
Both components (21)
(2 effusion present)
Glandular component only (12)
Parenchymal component only (17)
Pulmonary and extrapulmonary tuberculosis (15)
Primary pulmonary tuberculosis (14)
Reinfection tuberculosis (1)
Both components (9)
Glandular component only (4)
Parenchymal component only (1)
Extrapulmonary tuberculosis (6)
Total with diagnoses of active or "questionably active" tuberculosis.. (86)
(total of 3 groups above)
Total with diagnoses of possible tuberculosis (active)..... (4)
Total without diagnoses of active tuberculosis..... (8)
Total not in hospital more than 1 day and for whom diagnoses were not made ..... (2)
Total admissions ..... (100)

* Figures in parentheses indicate the number of cases.

either infiltration or consolidation in the upper lobes without tracheobronchial glandular components.

The criteria used to differentiate primary and reinfection tuberculosis are the age of the patient and the subsequent course of the lesion. Since the parenchymal components of the primary complex are frequently seen in the upper lobes, the site of the tuberculous lesions in these "doubtful" cases does not rule out primary disease. In general, the younger the patient, the more likely is the disease to be primary. Rarely does reinfection tuberculosis occur before the age of puberty.[1]

1. Miller, J. A., and Wallgren, A.: Pulmonary Tuberculosis in Adults and Children, New York, Thos. Nelson & Sons, 1939, p. 169.

The subsequent course of a lesion in reinfection tuberculosis is much more chronic and has much less tendency to change over the months than has that of a lesion of primary tuberculosis.

SUMMARY OF CASE MATERIAL

Vital Statistics.—Of the 100 patients, 44 were boys and 56 were girls. The oldest was a 13 year old boy; the youngest, three infants 9 months of age. Four patients were under 1 year of age; seven were 1 year old; 13 were aged 2 years; 11 were 3 years; 13 were 4 years; nine were 5 years; nine were 6 years; 14 were 7 years; three were 8 years; four were 9 years; seven were 10 years; four were 11 years; one was 12 years, and one was 13 years. Of the total group, 37 were Negro Americans, 26 were white Americans and 37 were white or Negro Puerto Ricans; of the 86 with proved tuberculosis, 33 were Negro Americans, 21 were white Americans and 32 were white or Negro Puerto Ricans.

Nineteen patients were admitted from home. The other 81 patients were admitted from other New York hospitals.

Four of the 100 patients represented readmissions.

Contact History.—A history of contact was elicited for 54 of the 100 patients admitted and for 46 of the 86 with proved tuberculosis.

Tuberculous History.—The histories elicited at this hospital are generally unreliable, since frequently there is a language difficulty (Puerto Ricans often speak only Spanish) and the parents frequently do not remember the history or do not present themselves in order to give a history. Usually we must depend on the transfer notes from the previous hospital.

In 15 of the 86 patients with proved tuberculosis, no symptoms were elicited. The diagnoses were made on routine Board of Health check-ups for contacts. In 12 of the 86 with proved tuberculosis, a history of chronic productive cough was noted in the transfer summaries. Most of the patients had mild primary tuberculosis and had no cough in this hospital.

For 14 of the 86 patients with tuberculosis the diagnosis was made at another hospital during or immediately after an acute infection of the upper or lower respiratory tract. In 12 of the 86 patients extrapulmonary signs (for example, enlarged cervical nodes, limp, etc.) were the only manifestations of tuberculosis observed. Frequently pulmonary lesions were detected when the children were examined.

Diagnosis.—Roentgenography was the chief aid in diagnosis. Roentgenologic technic is important. An upright 6 foot (1.8 meter) film, preferably taken during an inspiration, is required for accurate inter-

pretation of the chest film. Symptoms were usually of no help in diagnosis and physical examination was usually equally unrewarding.

Of the 100 cases, 99 of the patients had a positive tuberculin skin reaction on admission. The one patient who had a negative tuberculin skin reaction had an abnormal mediastinal density on roentgenogram. The patient was operated on and a mediastinal mass, which on section proved to be a ganglioneuroblastoma, was removed. The patient was discharged immediately after operation.

According to Myers,[2] a positive tuberculin skin reaction in an infant indicates active tuberculosis but in an older child does not necessarily indicate tuberculosis, even when accompanied with pulmonary disease. A 7 year old boy was admitted who had a positive tuberculin skin reaction, a history of pulmonary abnormality on roentgenogram which had entirely cleared within a few months and a history suggestive of atypical pneumonia at the time of roentgenography. This patient was discharged as having a cleared atypical pneumonia. The other six patients with the diagnosis of not having active tuberculosis were older children who had positive tuberculin skin reactions but no pulmonary disease demonstrable by roentgenogram and no evidence of activity.

Biopsy of material from, for example, the cervical nodes, was another aid in diagnosis. Demonstration of the tubercle bacillus in the body (for example, in the excretions, sputum, urine, feces, gastric contents or cerebrospinal fluid) is the only definite proof of tuberculosis. This problem will be discussed subsequently.

The longest period between diagnosis and transfer to this hospital was two years. Frequently a child had been transferred immediately after diagnosis. The average period between diagnosis and transfer to Sea View was four months.

Constitution.—The admission age and weights of 91 of the 100 patients (no weights were obtained on the nine other patients) were projected onto the age-weight graph prepared by the department of pediatrics of the State University of Iowa. Thirteen patients were above the sixteenth percentile or above the "normal limits" of weight for age. Forty-seven patients were between the sixteenth and eighty-fourth percentile or within the "normal limits"; 21 of this group were above the median and 26 were below. Thirty-one patients were below the eighty-fourth percentile, or below "normal limits."

The children admitted were below the "normal" children in weight. Certainly, since these children were from a lower economic group one would expect that their average weight would be somewhat below the "normal." In the hospital the children on a proper diet gained rapidly and came within the "normal" range, although the other forms of

2. Myers, J. A., and others: Tuberculosis Among Children and Young Adults, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1938, p. 90.

therapy should be considered as factors in their rapid weight gain. The point to be made is that the majority of these tuberculous children were not markedly underweight on admission.

Roentgen examination of the wrists for osseous development was performed on admission. Of 92 patients examined (no report was made on eight patients), 76 had normal osseous development and 16 had retarded development. No correlation was noted between osseous development and the weights of the children. Also, no correlation was noted between the osseous development and the severity of the tuberculous process.

Pulmonary Findings.—Atelectasis was definitely noted in five patients on admission. All five had primary complex tuberculosis (either parenchymal and glandular components or only the parenchymal component demonstrable by roentgenogram).

Extrapulmonary Findings.—The following are the extrapulmonary complications found present in the 86 proved cases of tuberculosis. More than one "complication" was not infrequently present in the same patient. Cervical adenitis was present in seven cases; meningitis, in four cases; tuberculosis of vertebra (Pott's disease), in six cases; arthritis of hip, in three cases; arthritis of knee, in two cases; dactylitis, in one case, and phlyctenular conjunctivitis, in one case.

These complications were either present when the diagnosis of tuberculosis was made or occurred within six months after the diagnosis, with one exception of which we were aware. In this patient, with only tracheobronchial glandular involvement on admission to this hospital and with eight months of previous hospitalization, a tuberculous hip developed after six months in this hospital, at the time when he was about to be discharged.

Nontuberculous Conditions.—The following list indicates the nontuberculous conditions diagnosed in the 86 cases of proved tuberculosis: congenital syphilis (two cases), strabismus, talipes equinus, congenital dislocated hip, situs inversus, mongolism, congenital heart disease, congenital cataracts, hypertension (of undetermined origin) and herpes zoster.

Laboratory Data.—On admission four patients with hemoglobin levels of less than 10 Gm. (9.5, 9, 9 and 8 Gm.) per 100 cc. were observed. These four patients along with a fifth patient had red blood cell counts of less than 3,500,000 cells per cubic millimeter (3,300,000, 3,300,000, 3,100,000, 3,000,000 and 2,800,000). The majority of patients had hemoglobin levels of about 12.5 Gm. per 100 cc. and red blood cell counts of about 4,200,000 per cubic millimeter.

No consistent leukocytosis or shift to the left was observed.

Sedimentation rates (corrected) were observed to be unreliable guides as to activity or to progress. According to Miller and Wallgren,[3] an increased sedimentation rate and an elevated temperature frequently occur concomitantly in tuberculosis. Since the majority of our patients had no fever, even on admission, it was no surprise to find that the majority had normal sedimentation values. Miller and Wallgren stated that "one is not justified in drawing any prognostic conclusions from the rate of the sedimentation alone."[3]

In the children's division of Sea View Hospital cultures for tubercle bacilli are not routinely performed. Smears of concentrated gastric lavage contents are the usual means of identification of the tubercle bacilli. Routinely, three smears of the concentrated gastric contents are made on admission, and one smear of the concentrated gastric contents of every patient in the hospital is made monthly.

Of the 86 patients with proved tuberculosis, three had one smear positive for Mycobacterium tuberculosis. All three patients had the "usual" primary complex, in which the discovery of a positive smear was unpredicted. Immediate subsequent smears were negative in all three cases.

Three other patients had more than one smear positive for Myco. tuberculosis. In these three cases—a progressive primary, a reinfection with cavity and a spread of a primary complex—the positive gastric smears were predicted.

In one other case—a case of miliary tuberculosis—tubercle bacilli were suspected in the gastric contents. Repeated gastric smears were negative for the bacilli, but when a culture was performed it revealed the presence of tubercle bacilli. This finding is no surprise, since, as Pinner [4] pointed out, when cultures of gastric contents are performed when repeated smears of the gastric contents have been negative an appreciable number of cultures will be positive for tubercle bacilli.

A program to make fewer smears of gastric contents and to perform more cultures when the presence of tubercle bacilli in the gastric contents is suspected is being discussed by the attending staff of the children's division of Sea View Hospital. We believe that monthly performance of gastric lavages on every patient in the hospital is a useless, traumatizing procedure.

Course in Hospital.—The general criteria for discharge of a tuberculous patient at the children's division of Sea View Hospital are (1) general well-being of the patient (that is, normal temperature, freedom from symptoms and physical findings of tuberculosis, adequate weight

3. Miller and Wallgren,[1] p. 139.

4. Pinner, M.: Pulmonary Tuberculosis in the Adult, Springfield, Ill., Charles C Thomas, Publisher, 1945, pp. 355-364.

gain and absence of anemia) for at least a three month period; (2) absence of tubercle bacilli in the gastric contents or sputums; (3) absence of active extrapulmonary tuberculous lesions; and (4) either absence of pulmonary lesions demonstrable by roentgenograms over a period of three months or minimal pulmonary lesions demonstrable by roentgenograms with no change over a period of six months.

A summary of the course in this hospital (for eight to 14 month periods) of the 86 proved cases and four doubtful cases of tuberculosis follows.

I. Pulmonary tuberculosis (only) 65 cases

A. Primary pulmonary tuberculosis, 53 cases

1. Primary complex, 50 cases

a. Both glandular and parenchymal components, 21 cases

6 cases, not much change on the roentgenogram (one patient signed out against advice)

4 cases, clearing but moderate lesion was still present on the roentgenogram

7 cases, clearing and only minimal lesions still present on the roentgenogram; should be ready for discharge in several more months

4 cases, discharged from 10 to 14 months after admission

b. Glandular component only, 12 cases

6 cases, about ready to be discharged (one patient signed out against advice)

6 cases, discharged from eight to 12 months after admission

c. Parenchymal component only, 17 cases

4 cases, not much change on the roentgenogram

8 cases, clearing and only minimal lesion still present on the roentgenogram; should be ready for discharge in several more months

3 cases, about ready to be discharged

2 cases, discharged from five to 13 months after admission

Four of these 50 patients were treated with streptomycin; three were treated in the previous hospital, and the fourth was treated in this hospital.

2. Progressive primary tuberculosis, 1 case

A 9 month old white girl was hospitalized for six weeks previous to hospitalization here. She received streptomycin intramuscularly and thiazolsulfone (promizole®) daily throughout her six week stay in the previous hospital. Roentgen examination on admission showed consolidation in the upper lobe of the left lung, with several suspicious cavities, and a 4 cm. cavity in the dorsal segment of the lower lobe of the left lung. Gastric smears throughout her stay in Sea View and one culture were negative for tubercle bacilli. She received streptomycin by aerosol only (streptomycin by aerosol is being evaluated at Sea View Hospital at the present time). Complete clearing and disappearance of the cavities within four months after admission were noted. The patient was signed out against advice two months later as having a quiescent case of tuberculosis.

3. Miliary, 2 cases

The first patient had had no previous hospitalization. He received streptomycin by aerosol and intramuscularly in Sea View, with complete

clearing of the pulmonary lesions on the roentgenogram within six months after admission. Gastric smears have all been negative for tubercle bacilli, but a culture on admission was positive for tubercle bacilli. The patient is still being followed in this hospital 14 months after admission.

The second patient received intramuscular injections of streptomycin daily during two months of his previous hospitalization, and he received streptomycin intramuscularly and by aerosol in Sea View. On the roentgenogram at present there is clearing, but miliary and primary complex lesions are still observed. Gastric smears and cultures have never revealed tubercle bacilli.

B. Reinfection tuberculosis, 4 cases

All four patients had received streptomycin intramuscularly and pneumothorax for cavity closure in the previous hospitals. The pneumothoraxes are being maintained. All 4 patients have always had negative gastric smears and cultures in this hospital.

Two patients are to be discharged shortly to be followed as outpatients and to be given regular pneumothorax refills.

One of the other two patients had a homolateral effusion when a pneumothorax on the right side was being discontinued. Streptomycin was given intramuscularly because it was feared that tubercle bacilli infection of the pleura was present. Smears of the pleural fluid have not revealed tubercle bacilli, but the results of cultures and guinea pig inoculations have not yet been reported.

C. Doubtful Tuberculosis, 8 cases

1. Primary pulmonary tuberculosis (probably), 2 cases

Minimal lesions with no change on the roentgenogram; both patients discharged within six months after admission.

2. Reinfection tuberculosis (probably), 6 cases

2 cases, slight spread on the roentgenogram

2 cases, no change or slight clearing on the roentgenogram. One of the two patients received streptomycin intramuscularly and by aerosol because of a possible cavity in the upper lobe of the left lung. All gastric smears have been negative for tubercle bacilli. On roentgen examination no change has been noted.

1 case, minimal lesion on the roentgenogram on admission (signed out against advice one month after admission)

1 case, the patient is almost ready for discharge. The patient received intramuscular injections of streptomycin for a bronchogenic spread, which has cleared since the institution of streptomycin therapy. Gastric smears have always been negative for tubercle bacilli.

II. Pulmonary and Extrapulmonary Tuberculosis, 15 cases

The pulmonary lesions in this section of the summary are not discussed in detail, since the problems of the pulmonary lesions in this group are the same as those reviewed in the section above.

A. Cervical nodes and primary complex, 5 cases

Three patients had histories of tuberculous cervical nodes in the previous hospital but had no evidence of active tuberculous cervical nodes in this hospital. All three patients received streptomycin intramuscularly in the previous hospital. Two of these patients also had surgical removal of cervical nodes. (The other patient received streptomycin intramuscularly for spread of a primary complex, with good results.)

Two patients were admitted to this hospital with active tuberculous cervical nodes. Both received streptomycin intramuscularly in the previous hospital and in this hospital. One had draining nodes on admission which healed within six months and which have remained healed for the past four months. The other had draining nodes shortly after admission which healed on streptomycin therapy within a few months but began to drain again about five months ago and have drained since. The latter patient is again undergoing streptomycin therapy, and excision of the nodes is contemplated. Smears of the drainage from the nodes of both these patients were positive for tubercle bacilli.

B. Meningitis and primary complex, 2 cases

In the first case meningitis was diagnosed one week after admission to this hospital. Guinea pig inoculation of the spinal fluid was positive for tubercle bacilli. Treatment consisted in intrathecal and intramuscular injection of streptomycin and thiazolsulfone for the meningitis. No evidence of meningitis or sequelae of meningitis was noted six months after admission. There was recurrence of meningitis eight months after admission. The patient was treated again with intrathecal and intramuscular injections of streptomycin but died two months later. At the time of her death the pulmonary lesions appeared on roentgen examination to be resolving.

In the second case meningitis was diagnosed shortly after admission to this hospital. Guinea pig inoculation of the spinal fluid was positive for tubercle bacilli. Treatment consisted in intrathecal and intramuscular administration of streptomycin and thiazolsulfone for the meningitis. The patient recovered in a few months, and no evidence of meningitis or sequelae of meningitis has been noted during the past one year.

C. Tuberculosis of vertebra (Pott's disease) and primary complex, 4 cases

All four patients had fusions and received streptomycin intramuscularly in this hospital.

D. Hip and primary complex, 2 cases

Both patients received streptomycin intramuscularly and one patient had an arthrodesis in this hospital. The other patient will probably have an arthrodesis.

E. Dactylitis and primary complex, 1 case

The dactylitis cleared on intramuscular streptomycin therapy. The patient was signed out against advice eight months after admission, but at that time the symptoms, signs and roentgenogram evidence of dactylitis had cleared.

F. Knee and reinfection tuberculosis, 1 case

Arthrodesis of the knee was done during the previous admission. No active tuberculosis in the knee has been demonstrated during the present admission. On readmission the patient had a large cavity in the upper part of the right lung. Pneumothorax on the right side was attempted but was unsuccessful. Pneumoperitoneum was instituted and is being maintained. In addition, the right phrenic nerve was crushed. The patient had received streptomycin therapy in the previous hospital and received streptomycin by aerosol in this hospital. Sputum smears remained positive for tubercle bacilli throughout the hospital stay. The patient has improved clinically, but the pulmonary lesions on roentgenograms have remained unchanged. At present the case is being evaluated, and other forms of therapy are being considered.

III. Extrapulmonary Tuberculosis (only) 6 cases

A. Cervical nodes, 1 case

The patient received streptomycin for tuberculous cervical nodes in the previous hospital. The nodes began to drain eight months after admission to this hospital. Streptomycin treatment was instituted and the drainage stopped about three months after it had begun. No evidence of active tuberculous nodes for the past three months has been noted.

B. Tuberculosis of vertebra (Pott's disease) and meningitis, 2 cases

In one case meningitis developed shortly after a spinal fusion in this hospital. Guinea pig inoculation of the spinal fluid was positive for tubercle bacilli. The patient received streptomycin and thiazolsulfone intramuscularly and intrathecally for the meningitis. There has been no evidence of meningitis or sequelae of meningitis for the past 10 months.

The other patient had a spinal fusion and was treated for tuberculous meningitis in the previous hospital. He has mental retardation at the present time, but it is not known whether or not he was mentally retarded before the onset of meningitis.

C. Tuberculosis of vertebra (Pott's disease), 1 case

In this hospital streptomycin was administered and spinal fusions were performed.

D. Knee and phlyctenular conjunctivitis, 1 case

In this hospital streptomycin was administered, and an arthrodesis was performed. Phlyctenular conjunctivitis developed in this hospital. The conjunctivitis has cleared without sequelae.

E. Hip, 1 case

In this hospital streptomycin was administered and arthrodesis is to be performed.

IV. Doubtful Tuberculosis, 4 cases

A. Pleural effusion, 1 case

The effusion cleared six months after admission. Tuberculosis has not been proved. The patient is being considered for discharge.

B. Sinus of thigh, 1 case

Biopsy was not performed. The patient received streptomycin therapy. No change in the skeletal system was noted on the roentgenogram. The sinus closed a few months after admission, and the patient was discharged six months later.

C. Multiple large cysts of left lung, 1 case

The cysts are probably congenital, but tuberculosis has not been eliminated as a possibility. The patient is being prepared for surgery.

D. Arthritis of knee, 1 case

Tuberculosis could not be proved. Biopsy did not reveal tuberculosis, and the patient was discharged six months after admission.

Treatment.—At this hospital the following factors in the treatment of tuberculosis in children are observed: rest, diet, psychological therapy, drugs, surgery and special tests.

1. *Rest.*—Activity varies from complete bed rest to full activity, depending on the condition of the patient. Most of the children at Sea View Hospital are on full activity. Isolation technic is used when the patient is infective, that is, when smears or cultures of the sputum or gastric contents are positive for tubercle bacilli.

2. *Diet.*—A high calory, high protein diet with supplemental vitamins is provided.

3. *Psychological Therapy.*—Psychological therapy is a very important factor in treatment. Recreation and school facilities are available, and the entire hospital personnel is instructed in psychological technic. However, much remains to be desired for an adequate coverage of the needs of the patients for psychological therapy.

4. *Drugs.*—The drugs used specifically at this hospital for the treatment of tuberculosis are streptomycin, thiazolsulfone (promizole®) and paraaminosalicylic acid. Streptomycin appears to be the most effective drug, but a combination of streptomycin with either thiazolsulfone or paraaminosalicylic acid appears to be more effective than streptomycin alone. A combination of streptomycin with either one of the two drugs appears to delay development of drug resistance.

Thirty-five of the 100 patients reported on were treated with streptomycin; 27 of these 100 patients were treated with streptomycin in this hospital.

A combination of streptomycin with either thiazolsulfone or paraaminosalicylic acid is used for the following types of pulmonary tuberculosis (general indications with variations in individual cases): (1) miliary tuberculosis; (2) progressive primary tuberculosis; (3) pulmonary tuberculous lesions demonstrable roentgenographically in children under 2 years of age; (4) spread of a progressive primary tuberculosis (frequently therapy is delayed to permit observation of the lesion without drug therapy); (5) endobronchial tuberculosis, and (6) advanced pulmonary tuberculosis.

A combination of streptomycin with either thiazolsulfone or paraaminosalicylic acid is used for the following types of extrapulmonary tuberculosis (general indications with variations in individual cases): (1) tuberculous cervical nodes (surgery is frequently indicated in chronic cases); (2) tuberculous meningitis (streptomycin is given intrathecally in association with intramuscular administration of streptomycin and either thiazolsulfone or paraaminosalicylic acid); (3) orthopedic tuberculosis—e. g., of the spine, hip or knee, dactylitis, etc.—(the combination of early operation and administration of streptomycin used in this hospital for treatment of orthopedic tuberculosis appears to produce very favorable results); (4) other complications—e. g., gastrointestinal tuberculosis, etc.

Toxic reactions to streptomycin are infrequently observed in the children's division of Sea View Hospital, but drug resistance is not infrequently observed when streptomycin is given over a prolonged period.

The exact courses of treatment are not described because at this hospital Lincoln and Kirmse's courses of treatment [5] are used with very little modification.

5. *Surgical Procedures.*—Surgical procedures are frequently resorted to in this hospital. Five of the 86 patients with proved tuberculosis were being maintained on collapse therapy. All five patients had reinfection tuberculosis, with cavity disease. Pneumothorax is the usual method of collapse, but one patient was being maintained on pneumoperitoneum.[6] Pulmonary resections have been performed on a few of the patients in this hospital but on none of the patients in our series.

6. *Special Tests.*—Special tests, such as bronchoscopy, bronchography and gum biopsy, are not infrequently performed to determine the status of the patient. Bronchoscopy is of special value in detecting endobronchial tuberculosis. In some patients, especially those who have had atelectasis, bronchography frequently reveals bronchiectasis. None of these patients with roentgen evidence of bronchiectasis have had symptoms or physical findings of bronchiectasis.

Gum biopsy for the detection of amyloid disease is performed at this hospital. The congo red test, because of its toxicity, is not used at Sea View Hospital. No cases of amyloid disease have been observed in the past year.

COMMENT

Primary complex disease roentgenologically does not necessarily disclose both a parenchymal component and a tracheobronchial component. In over half of the cases in the primary complex group only one or the other of the two components was demonstrable by roentgenogram. In these cases the parenchymal component appeared slightly more frequently than the tracheobronchial component.

Very few cases of progressive primary and miliary disease were observed. This observation can be explained by the fact that in the other hospitals from which our patients are admitted there is a tendency to treat these patients and to transfer to Sea View Hospital only the less seriously ill patients. Reinfection tuberculosis is seen in children, and frequently the distinction between primary and reinfection tuberculosis is difficult. Extrapulmonary disease was observed in one quarter of the 86 patients with proved tuberculosis. In almost one third of this group no pulmonary disease was demonstrable by roentgenograms.

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5. Lincoln, E. M., and Kirmse, T. W.: Chemotherapy of Tuberculosis in Children, Pediatrics **5**:280 (Feb.) 1950; Streptomycin-Promizole Therapy of Miliary and Meningeal Tuberculosis in Children, Am. Rev. Tuberc. **61**:159 (Feb.) 1950.

6. Wassering, J. D.: Medical Progress: Tuberculosis, New England J. Med. **240**: 463 (March 24) 1949.

A high proportion of Puerto Ricans are admitted to the children's division of Sea View Hospital. Measures to reduce the high incidence of tuberculosis in Puerto Ricans should be more vigorously implemented; perhaps BCG immunization might be of value. In over half of the cases a history of contact was elicited. A reduction in the number of adults with infective tuberculosis who are allowed to carry on at home without taking adequate precautions would reduce the incidence of tuberculosis in children.

In the diagnosis of tuberculosis roentgenography was the chief aid. A tuberculin skin test was also important. In all the patients with active tuberculosis a positive tuberculin skin reaction was present. The physician should hesitate to diagnose tuberculosis in the absence of a positive tuberculin skin reaction, provided the test is accurately performed and the tuberculin is in the proper concentration. However, a positive tuberculin skin reaction does not indicate active tuberculosis except in infants.

On admission these patients were not markedly underweight, and no correlation was noted between the osseous development of their wrists and the severity of the tuberculous process.

Tubercle bacilli were detected in the gastric contents of only a few patients. However, cultures of the gastric contents appeared to be much more reliable than smears of the gastric contents in the detection of the tubercle bacillus, and we believe they should be performed more frequently.

The criteria for discharge at this hospital have been outlined, but they do not always apply in private pediatric practice. The majority of the patients in the children's division of Sea View Hospital could be adequately managed at home provided the patient could receive sufficient and intelligent home care. Generally, for the mental health of the patient it is preferable to treat the child at home. The only reason for hospitalization is the lack of essential facilities in the home that are provided in the hospital. Even the identification of tubercle bacilli in gastric contents or sputum, a rare occurrence in children, is no absolute contraindication to home management.

Streptomycin and the other specific antibiotics are important in the treatment of tuberculosis and are justifiably receiving much attention at present. However, in less than one third of the cases was streptomycin considered to be of sufficient therapeutic value to be administered. One cannot exclude the other factors in therapy which are as important as the antibiotics.

SUMMARY

One hundred consecutive admissions during 1949 to the children's division of Sea View Hospital have been reviewed. The following features are discussed: diagnoses, vital statistics, contact history, symp-

toms, diagnostic procedures, constitution, pulmonary findings, extrapulmonary findings, laboratory data, course in the hospital and treatment.

An attempt is made to clarify practical clinical problems of tuberculosis in children and to present to the physician the picture of tuberculosis as it is seen in the wards of a large tuberculosis hospital for children.

Dr. Maurice Small aided in this study.

INFANTILE AND ATOPIC ECZEMA FROM INJURY TO THE SKIN BY OVERCARE AND OVERTREATMENT

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LOCAL and generalized dermatoses are common, owing to the application of therapeutic chemicals to the skin.[1] One report disclosed an incidence of overtreatment of 35 per cent [2] and another 75 per cent.[3] When the irritating and sensitizing chemicals were removed, as a rule prompt healing of the lesions took place. In some cases, however, lesions healed slowly, indicating a severer chemical injury to the skin. In others the patients appeared to have recovered but complained about dryness, roughness, redness, chapping in cold weather and ease of irritation. Soap would burn, and exposure to sunlight caused itching and hiving. Many patients, when seen long after their dermatitis had healed, noted itching, burning and transitory rashes when they became warm enough to perspire. A complaint that is heard more and more is, "When I get hot I itch and break out." This cutaneous injury from exposing the skin to varieties of chemicals may be the "sweat retention syndrome." [4] A sulfonamide sensitization can leave this sequela. Alarm is sensed because drugs used on the skin or chemicals in soap, clothing and footwear [5] may be damaging the temperature-regulating functions of the body. These are serious injuries. They can disable a person in hot weather and may cause death.

Searching for sequelae from overtreatment paved the way for a significant observation.

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1. Gaul, L. E.: Overtreatment Dermatitis, J. A. M. A. **127**:439 (Feb. 24) 1945.

2. Underwood, G. B.; Gaul, L. E.; Collins, E., and Mosby, M.: Overtreatment Dermatitis of the Feet, J. A. M. A. **130**:249 (Feb. 2) 1946.

3. Underwood, G. B., and Gaul, L. E.: Overtreatment Dermatitis in Dermatitis Venenata Due to Plants, J. A. M. A. **138**:570 (Oct. 23) 1948.

4. Sulzberger, M. B.; Herrmann, F., and Zak, F. G.: Studies of Sweating, J. Invest. Dermat. **9**:221 (Nov.) 1947.

5. Gaul, L. E., and Underwood, G. B.: Primary Irritants and Sensitizers Used in Fabrication of Footwear, Arch. Dermat. & Syph. **60**:649 (Nov.) 1949.

D. C. (case 1, table 1) was seen because of an eruption involving the face and flexor surfaces of the extremities. The onset was in October 1949; the weather was dry and cold. The distribution was limited to the exposed areas of skin. All areas of the skin covered by clothing were normal. The history revealed that the child had had a normal skin until 6 months of age. In February 1949 her left leg was burned on a stove. A popular burn ointment, containing 10 different chemicals, was applied. Two weeks later, the incubation period for sensitization, there was an eruption at the site, and overnight a dermatitis appeared on the face and extremities. Various topical remedies and changes in the formula did not affect the course. During the spring of 1949 and as the weather warmed, the eruption improved, and by June the skin was apparently normal. Cold weather in the fall brought a recurrence.

A reconstruction of the clinical events in this case suggested a new concept of atopic dermatitis. A sequela of the generalized dermatitis was apparently an increased susceptibility to cold. In the broader sense, the dermatitis left a residual injury to the peripheral vascular system, which accounted for the chronicity when cold put a stress on the skin. A thermal injury had disrupted the protective horny sheath. Chemicals in the burn ointment contacted living skin, which is ideal soil for sensitizers to undergo incubation. The generalized dermatitis was produced in cold weather and persisted until the weather got warm. Doubtless, certain sensitizing chemicals affect the physiological responsiveness of the peripheral vascular system to environmental stresses.

The age distribution and the severity of symptoms and signs suggested a reorientation of atopic dermatitis on the basis of the degree of chemical injury to the peripheral vascular system. The infantile type is an example of primary sensitization signs.[6] Soap and water is a common cause. Patch tests with 5 per cent aqueous soap solutions commonly produce a parchment-like reaction. The epidermis is changed into an easily fractured membrane. Beneath this is a brilliant erythema which may persist several weeks to months. Soap and water apparently produces a chronic vasodilatation. Add to this injury the vasodilatation from cold weather and the stress becomes sufficient to produce an eczematization. Any persisting vasodilatation disturbs normal keratinization and, in turn, may affect the integrity of the epithelial mantle and its ducts. Infants commonly have the involvement only on exposed areas of skin, such as the face. A chemical injury to the skin from soap and water, oils and lotions or overcare is the subthreshold groundwork for the stressing effects of the environment. Many of these patients get well without further recurrence, probably owing more to chance than to anything else. Some of them become candidates for the childhood type of atopic dermatitis. These children have had their primary sensitization signs sufficiently

6. Gaul, L. E., and Underwood, G. B.: Dermatitis Venenata from Organomercurial Compounds, J. A. M. A. **140**:860 (July 9) 1949.

overtreated so that secondary sensitization signs * have been produced. That is, their entire cutaneous vascular bed has been sensitized. Not only is their peripheral vascular system susceptible to sudden changes in the environment, but systemic factors which cause peripheral vasodilatation, such as psychic stimuli, exercise, food ingestion and others, also produce symptoms and signs. The third type, or adolescent form, is the classic sequela of overtreatment. The severe cases of this type have had their peripheral vascular system exquisitely sensitized. Minimal stimuli from the environment, such as air striking the face while riding in a car or embarrassment causing flushing of the face, produce attacks of burning, whealing, and itching. Numerous stimuli from without and within keep the skin in a constant state of turmoil.

Dermatologic textbooks and literature seldom discuss the circumstances immediately preceding the onset of dermatoses. This is due to the fact that dermatologists see the patients long after the onset—weeks, months or years. The day that symptoms and signs develop is a crucial time because the patient may be able to recall what happened on that day and in relating the events may inadvertently disclose the origin of the eruption. To see patients early would eliminate much needless suffering. Investigation of the factors that shifted a normal skin to abnormal is a fertile field for cutaneous research. Such a study was made in 18 cases of atopic dermatitis. The results are presented in table 1.

The ages varied from 3 months to 38 years. Ten patients were female and 8 were male. The age at onset ranged from birth to 36 years. The initial injury of the skin resulted from mechanical, thermal, physical or chemical agents. Every injury was promptly treated with some type of lotion, cream or ointment. These events are customary rather than significant. To apply the merosal merthiolate* to normal and to injured skin is customary, but it is significant that for some unknown reason a percentage of the users become sensitized. The time of onset of dermatitis is hard to interpret except from the standpoint of threshold or subthreshold vascular injury. In some of our cases the parents commented that the child's skin had become dry, rough, scaly and easily irritated from bathing. It may be that chemical irritants and sensitizers in affecting the integrity of cutaneous vessels also affect the function of the sweat and oil glands. The glands may even cease functioning to prevent penetration or absorption of noxious chemicals, or changes in the vascular bed may have keratinized their ducts and orifices. Four patients with rhinitis bring up an incidental observation. Chemical injury to the cutaneous vascular bed may induce abnormal responses in the respiratory mucosa, and an injured vascular bed is predisposed to viral and bacterial infections.

Of the persistent dermatoses only 3 were severe. J. S. and P. H. had tried every skin remedy known, which may be the reason for the severity of their responses. Many patients have remarked that when

TABLE 1.—*Initial Skin Injury or Dermatitis Followed by Overtreatment and*

Case	Age, Yr.	Sex	Age at Onset	Initial Injury or Dermatitis	Therapy Given	Dermatitis		
						Onset	Location	Behavior
1	2	F	6 mo.	Burn on left leg	"Brown ointment"	2 weeks later	Face, extremities	.....
2	24	M	7 yr.	Rhus dermatitis on right hand	"Blue lotion"; "brown ointment"	3 months later in fall	Face, extremities; rhinitis	Persistent
3	6	M	Birth	Circumcision; cradle cap	"White ointment"	10 days	Generalized; rhinitis	Persistent
4	3	F	8 mo.	Rash from baby oil	"Lanolin cream"	2 months later in fall	Face, extremities	.....
5	¼	F	6 wk.	Rash from soap on face	"Lanolin lotion"	2 weeks	Generalized	.....
6	¼	M	6 wk.	Rash about navel	"Lanolin lotion"	1 month	Generalized	.....
7	32	M	Birth	Circumcision	"White ointment"	Few days	Penis	Cleared at age 8
			15 yr.	Sunburn	"Tan ointment"	2 months	Generalized	Persistent
8	11	M	6 yr.	Cut on forehead	"Tan ointment"	2 months	Forehead, upper extremities	.....
9	28	M	26 yr.	Rash on right forearm, weeds?	"White ointment" (sulfanilamide?)	2 weeks	Face, upper extremities; rhinitis	Persistent
10	22	F	18 mo.	Scratch from screen door	"White ointment"	10 days	Generalized; rhinitis	Persistent
11	16	F	7 yr.	Cut on right leg, skating	"Yellow ointment"	3 days	Face, extremities	.....
12	8	F	6 mo.	Scratch from fall	"Lanolin cream"	2 weeks	Face, extremities	.....
13	¼	M	6 wk.	Baby oil antiseptic	"Gray ointment"	5 days	Face	.....
14	20	M	8 mo.	Impetigo?	"White ointment"; "purple liquid"	1 month	Generalized; rhinitis	Persistent
15	3	F	1 yr.	Scratch on right knee	"Tan ointment"	2 months	Face, extremities	.....
16	2	F	Birth	Insect bite	"White ointment"	1 month	Face, upper extremity	.....
17	3	F	5 wk.	Baby oil antiseptic	"Brown ointment"	6 days	Face, extremities	.....
18	4	F	1 yr.	Rash from soap	"Green ointment"	1 month	Face, upper extremities	.....

they stopped all treatment they gradually got better. T. R. possibly had a sulfonamide sensitization. Ten patients had apparently normal skins during the summer; cold weather was their nemesis. The history of relatives and parents suggests that these patients inherited a vascular bed highly susceptible to chemical injury and cold. Among the siblings in the 18 cases were 19 sisters and 28 brothers unaffected. P. H., and

C. H. (cases 5 and 6, table 1) were dissimilar twins. They were born in the hospital, and the mother was given samples of a baby soap and lotion. Their seven brothers and sisters with normal skins were born at home.

Susceptibility to Cold with Resulting Symptoms and Signs of Atopic Dermatitis

Season of Remission	Season of Recurrence	Familial History			Treatment	Results of Treatment
		Relatives	Parents	Siblings		
Summer	Fall	Maternal aunt, eczema	.....	1 sister, well	Cotton union suits	Excellent
Mild in summer	Severe in winter	.....	Father, mild asthma	1 sister, winter eczema on hands; 2 sisters, 2 brothers, well	Cotton union suits	Excellent except for face and rhinitis
Mild in summer	Severe in winter	Paternal grandfather, hay fever	Mother, winter eczema on hands	1 sister, 3 brothers, well	Cotton union suits	Excellent except for marked dryness of skin in winter
Summer	Fall	Maternal cousin, eczema	.....	3 brothers, well	Cotton union suits	Not known; observed only once
.....	Fall	.....	Mother, winter eczema on hands	3 sisters, 4 brothers, well	Night caps and union suits	Excellent
.....	Fall	.....	Mother, winter eczema on hands	3 sisters, 4 brothers, well	Night caps and union suits	Excellent
Summer	Fall	.....	Mother, eczema	.....	.....	.....
Mild in summer	Severe in winter	.....	.....	.....	.....	Well except for slight flare-ups on face
Summer	Fall	.....	Mother, itching and hives after hot bath	.....	Cotton-lined helmet, union suits	Excellent
Mild in summer	Severe in winter	.....	.....	4 brothers, 3 sisters, well	Union suits	Excellent
Mild in summer	Severe in winter	.....	Father, rhinitis; mother, eczema on hands in winter	2 sisters, well	Cotton bonnet and union suits	Excellent
Summer	Fall	Maternal aunt, eczema	Father, rhus dermatitis	1 sister, brother, well	Shirtwaists	Excellent
Summer	Fall	Maternal grandmother, eczema	Father, eczema on hands in winter	2 brothers, 2 sisters, well	Union suits	Excellent
.....	Fall	.....	.....	1 sister, well	Cotton helmet	Excellent
Mild in summer	Severe in winter	.....	Father, eczema on hands in winter	3 brothers, well	Cotton union suits	Not known; only one return visit; lived in South
Summer	Fall	.....	Father, eczema on hands in winter	1 brother, well	Cotton helmet and union suits	Excellent
Summer	Fall	.....	.....	1 sister, well	Cotton union suits	Excellent
Summer	Fall	.....	.....	1 sister, 1 brother, well	Cotton union suits	Excellent
Summer	Fall	.....	Father, eczema on hands in winter	3 brothers, well	Cotton union suits	Excellent

They had minimal care; the twins, overcare. The formula of one of the baby oils mentioned has been changed three times in four years. One mother brought in a box of baby powder, oil and soap which contained an antiseptic that is known to be a powerful sensitizer. Patch tests were done in three cases with the original therapeutic agents. The appearance within 24 hours of a generalized rash caused such concern

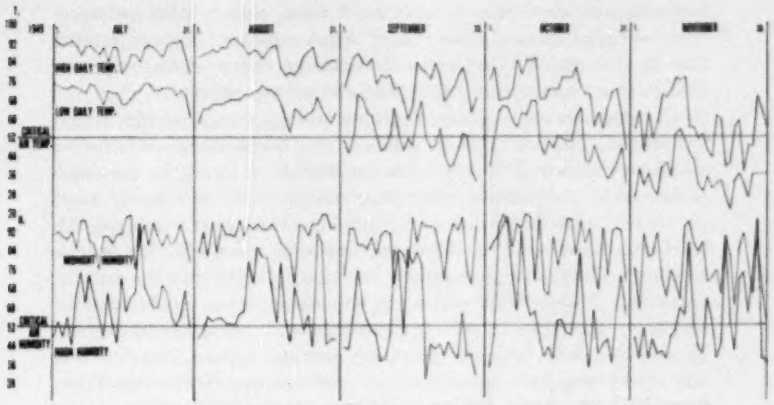
that testing was stopped. J. S. (case 2, table 1) was certain he could identify the oily, brown ointment that was used prior to the onset of his dermatitis if he could smell it. The local druggists allowed us to inspect their ointments. Finally, it was found; a mixture of sulfides of zinc in wool fat and petrolatum. He recognized the odor, and a bit of it on his skin caused burning, erythema and pinpoint vesicles. Some of the ointments applied had had a shelf life of years. Deterioration products, highly sensitizing, were suspected.

Early in the fall of 1949 an effort was made to correlate the onset, recurrences and exacerbations in atopic dermatitis with weather changes. The findings are shown in figure 1. The critical air temperature seems to be 52 F. and the humidity 52 per cent. In July and August 1949 there were only 11 days in which the humidity fell below 52 per cent. In September the temperature fell below 52 F., and there were proportionately more days of humidity below 52 per cent. During October home heating was necessary, which decreased the room humidity; in such circumstances the person becomes subjected to extremes of both temperature and humidity. At these extremes, moisture is removed from the skin like the evaporation of a drop of water on a hot stone. Water on the skin evaporates so fast that excessive cooling and persistent vasodilatation result. Adult skin chaps at these extremes. The critical weather continues until the following summer. A study of this figure makes it difficult to understand why a food or formula eaten in October should produce lesions, whereas the same when eaten in July is highly nutritious in the atopic persons. The observations in table 1 and figure 1 provide evidence that in atopic dermatitis there is an underlying susceptibility to sudden changes in weather.

The location of atopic eczema confirms the susceptibility to cold. Babies are seen with only their faces involved. The covered areas of the skin appear normal. Children are seen with only their faces and forearms involved. The covered areas of the skin appear normal. Other children have their face, forearms and legs involved, with the covered areas normal. Excepting the face and neck, the areas of distribution follow the fashion of dressing. D. K. (case 15, table 1) showed a severe involvement of the face, ears and upper extremities. Most of the time she wore overalls; the torso and lower extremities were normal. We must concede that our grandparents exercised good sense when with the onset of cool weather the long underwear was donned and worn until warm weather returned. The fashion in infants' and children's clothes should be dictated by the necessity to provide clothing which protects the cutaneous peripheral vascular system from injury by cold and dry weather.

The distribution of atopic dermatitis occurs in areas of the body having the greatest heat loss: face and flexor surfaces of the extremities.

When the extremities are flexed, the temperature of the apposed skin builds up to body temperature and some moisture usually accumulates. Extending the extremities causes sudden cooling, and flexion, sudden heating. An excess of heat produced by the body is dissipated first by



Subthreshold Weather		Threshold Weather		Critical Weather	
Cases Without Symptoms and Signs	Cases with Mild Symptoms and Signs	Cases with Initial Onset	Cases with Recurrences	Cases with Recurrences	Cases with Severe Recurrences
1. D. C.	2. J. S.			1. D. C.	2. J. S. Hospitalized twice during Jan. in South Dakota
	3. P. M.			3. P. M.	
				4. S. B.	
4. S. B.		5. P. H.			
5. P. H.		6. C. H.			
6. C. H.	7. R. G.		8. B. M.	9. T. R.	7. R. G. Hospitalized three times
8. B. M.	9. T. R.		10. J. M.	11. J. L.	10. J. M. Hospitalized once
10. J. M.				12. B. C.	12. B. C. Hospitalized once
11. J. L.					
12. B. C.					
13. D. P.		13. D. P.			13. D. P. Hospitalized once
14. P. H.	14. P. H.				14. P. H. Hospitalized many times had to live South in winter
15. D. K.				15. D. K.	
16. D. V.				16. D. V.	
17. S. D.			17. S. D.		
18. O. P.				18. O. P.	

Fig. 1.—Correlation of weather with onset and recurrences of atopic dermatitis. Interpreting exacerbations on the basis of weather is easier and cheaper than changing the diet and trying the endless succession of topical remedies.

the upper extremities, and if this is not sufficient vasodilation occurs in the lower extremities. Atopic lesions are seen in the areas where these temperature shifts occur. Vasodilatation sufficient to cause edema produces itching and burning. Persisting vasodilatation can be followed by lichenification and pigmentation. When J. S. (case 2, table 1) came

under observation it was noticed that the areas of skin covered by his T-shirt and shorts appeared normal. Sweating occurred in these areas without symptoms, but itching and burning accompanied sweating in the involved areas. A normal skin sweating profusely is pale and cool. In contrast, a skin showing mild inflammation, especially chronic—or recurring with accompanying vascular changes—always itches and burns when sweating occurs. The stimuli which regulate body temperature play in and out of these mild inflammations and produce symptoms. This produces the psychosomatic state and not vice versa.

Coming from the cold into a warm room was associated with typical and reproducible attacks in the case of J. S. A normal person active in a cold environment feels a flush of heat, even to sweating, on entering a warm room. Adjustment takes place quickly. As soon as the warm air would strike the face of J. S., burning would start. Bringing his hand near his face, he could feel the heat being given off. Rubbing or washing his face gave some relief. It seemed to counteract the drawing sensation. Within 10 minutes or so tingling sensations would occur on the flexor areas of his arms and sometimes in the popliteal regions. Vasodilation was doubtless occurring here to further dissipate heat which had been built up outdoors to meet the particular temperature. After 15 to 20 minutes, itching would begin, always at the blotchy points on his face, and soon itching would appear on the forearms. The sequence was always the same: burning, whealing and itching. About 45 minutes was required for his body to adjust itself to the higher temperature. Wind intensified the attacks, owing to its greater cooling and drying action. Symptoms or signs did not occur when he went from a warm room to a cold environment. Reviewing his attacks brought out the amazing way in which he unknowingly lessened their severity. On disrobing he hurriedly got into bed; in the morning he dressed quickly; after taking a shower he dried and swiftly put on his clothes. In very hot weather he perspired without symptoms anywhere except on his face, neck and forearms. Drafts and changes in activity always produced itching on his face and forearms. Identical histories were obtained from R. G., T. R., J. M. and J. L. (cases 7, 9, 10 and 11, table 1).

The delicate responsiveness of the peripheral vascular system to stimuli can be compared to that of the iris of the eye. This smooth muscle body is remarkably sensitive to environmental, constitutional and psychic stimuli. Drugs given internally, and externally, produce marked actions and may cause dangerous sequelae. The peripheral vascular system at environmental temperatures of 24 to 30 C., is in the zone of normal physiological rest. Below 24 C. varying degrees of vasoconstriction take place. At about 30 C. vasodilation begins, and at higher temperature maximal dilation occurs. This is the zone of regulation of

body temperature by sweat evaporation. Blood is shunted for cooling into the extremities—regions of the body having a small mass compared to their surface areas. At low temperatures the reverse happens. In hot weather one sleeps with the extremities extended; the fingers separated to promote the greatest cooling. In cold weather, flexion occurs to conserve body heat. The thin skin of the hands and feet is a delicate peripheral thermostat. Many environmental and systemic stimuli constantly assail the normal vascular bed. The stimuli ebb and flow with the person unaware of them. The entire range of responses, forceful or barely perceptible, occur autonomically and without symptoms. Vasodilation occurring in the chemically injured vascular bed in atopic dermatitis produces the symptoms and signs. An example is J. M. (case 10, table 1), who was referred to a psychiatrist. An embarrassing question caused her to blush. Psychic vasodilatation occurring in her injured vascular bed produced a severe attack of burning and itching.

Overcare of the skin is that practice which is advertised to do good but statistically causes harm. It produces a high incidence of minor rashes and irritations. A good example is the care of the newborn skin. The daily soap bath defats the skin, causing erythema, dryness, roughness and disturbance in keratogenesis—subthreshold vascular injury. A baby oil is substituted for the natural skin lipids. It further dissolves out the lipids that the soap and water missed. This overcare perpetuates the pinkness of the newborn skin and accentuates dryness and redness. Minute fissuring and chafing of the epidermis is the result. The skin that has had overcare is susceptible to heat rashes and secondary infections; and weather changes to lower temperatures and humidities stress the vascular bed to the point of eczematization. The end result of overcare is that the skin is less able to withstand the sudden exigencies of weather changes.

Many mothers are seen with eruptions on their hands which appeared after caring for the new baby. The increased water, soap and oil load was too much. The chemical injury to the adult epidermis is more provocative for the infant epidermis. Apfel[7] has recommended that the vernix caseosa should not be removed. His method was instituted in 1927, and in 23,000 newborn no skin complications occurred. The babies did not get a bath until after the cord had come away. He recognized that this method of care avoided breaks in the superficial layers of the skin. Preserving the integrity of the epithelial mantle is the basis of good skin hygiene. This allegation may seem fantastic but wool fat is suspected to contain a chemical, perhaps an oxidation product, which can injure the vascular bed to such an extent that it reacts abnormally to cold.

7. Apfel, H.: A Simplified Method of the Care of the Skin of the Newborn, Arch. Pediat. **66**:131 (March) 1949.

TABLE 2.—*Responses in Atopic Dermatitis to Immersion of Forearm in Hot and in Cold Water* *

		Response to Hot Water				
		Immersion Time, Minutes				
Subject	Temp., C.	2	4	6	8	10
J. S. (case 2)	44	Wrinkling of finger tips	Mild redness, flexor area; itching, drawing	.....	Tingling at water line	Slight redness, flexor area
Control man, aged 40	44	Slight redness, flexor area	Mild redness	.....	.....	Slight redness, flexor area
B. M.	45	Wrinkling of finger tips	Tingling, "pins and needles"	Slight redness	Paling	Slight redness
Control man, aged 28	45	Slight redness, flexor area	Mild redness	.....	.....	Slight redness
R. G.	43	Wrinkling of finger tips	Slight redness flexor area	Pulling	Paling	.....
Control man, aged 42	43	Slight redness, flexor area	Mild redness	.....	Mild redness	.....
T. R.	45	Wrinkling of finger tips	Slight redness, flexor area	Paling	Tingling at water line	.....
Control man, aged 33	45	.....	Tense redness, flexor area	.....	.....	Tense redness
J. M.	49	Wrinkling of finger tips	Slight redness, flexor area	.....	Tense redness	.....
Control man, aged 24	49	.....	Slight redness, flexor area	.....	Slight redness	.....
J. L.	42	Wrinkling of finger tips; drawing; slight redness	.....	Paling; itching; drawing	.....	.....
Control girl, aged 16	42	.....	Slight redness	Mild redness	.....	Tense redness
B. C.	41	Wrinkling of finger tips; paling	Tense redness	.....	Paling; itching; drawing	.....
Control girl, aged 12	44	Wrinkling of finger tips	Slight redness	.....	Mild redness	.....

		Response to Air						
		Exposure Time, Minutes						
Subject	Temp., C.	5	10	15	20	25	30	35
J. S.	23	Goose skin; tingling; pulling; nasal blockage; desire to scratch	Paling	Pale	Dry	.....	.....	.....
Control man, aged 44	23	.....	Slight redness	.....	.....	.....	.....	.....
B. M.	25	Goose skin; pulling	Paling	Pale	Dryness	.....	.....	.....
Control man, aged 28	25	.....	Slight redness	.....	.....	.....	.....	.....
R. G.	24	Goose skin	Paling	Pale	Dryness	.....	.....	.....
Control man, aged 42	24	Slight redness	.....	.....	.....	.....	.....	.....
T. R.	23	Nasal blockage	Paling; drawing	Pale	Dryness	.....	.....	.....
Control man, aged 31	23	.....	Slight redness	.....	.....	.....	.....	.....
J. M.	25	Nasal blockage; goose skin; tense redness	Drawing; itching; paling	Tense redness, flexor surface of elbow	Paling; dryness	.....	.....	.....
Control man, aged 24	25	Slight redness	.....	.....	.....	.....	.....	.....
J. L.	27	Itching; drawing; dry	Tense redness	Paling	.....	.....	.....	.....
Control girl, aged 16	27	.....	Slight redness	.....	.....	.....	.....	.....
B. C.	26	Pale; colder than right forearm	Tense redness; warmer than right arm	Paling	Dryness	.....	.....	.....
Control girl, aged 12	25	Mild redness	.....	Light redness	.....	.....	.....	.....

TABLE 2.—*Responses in Atopic Dermatitis to Immersion of Forearm in Hot and in Cold Water* * — *Continued*

Response to Cold Water

Subject	Temp., C.	Immersion Time, Minutes: 2	4	6	8	10
J. S.	10	Nasal opening; slight redness	Thumping of branchial artery	Cold; numb; "pins and needles"	.....	Tense redness
Control man, aged 40	10	Aching; pain; tense redness	Pain gone	Tense redness	.....	Tense redness
B. M.	13	Aching; paling	Tense redness; numb	.....	Tense redness	.....
Control man, aged 28	13	Aching; pain; tense redness	Pain gone	.....	.....	Tense redness
R. G.	13	Aching; pain; goose skin	Slight redness	Pulling	Tingling at water line	Slight redness
Control man, aged 42	13	Aching; pain	Mild redness	.....	.....	Tense redness
T. R.	10	Nasal opening; aching; pain; goose skin	Pulling; numb	Slight redness	.....	Tense redness
Control man, aged 31	10	Aching; pain	Tense redness	.....	.....	Tense redness
J. M.	13	Aching; pain; nasal opening; numbness	Slight redness	.....	Slight redness	.....
Control man, aged 24	13	.....	Tense redness	.....	Tense redness	.....
J. L.	12	Aching; pain; goose skin	Tense redness	Aching	Mottled redness	"Feels cold all over"
Control girl, aged 16	12	Aching; pain	Tense redness	No aching	.....	.....
B. C.	13	Aching; numb; slight redness	Tense redness	Paling	Tense redness	.....
Control girl, aged 12	13	Aching; numb; tense redness	.....	.....	.....	.....

Response to Air

Subject	Temp., C.	Exposure Time, Minutes: 5	10	15	20	25	30	35
J. S.	23	Tingling; burning; tense redness	Paling; warmer than right forearm	Flexural whealing at water line	Swelling of arm	Tense whealing	Boardlike edema	Subsiding
Control man, aged 40	23	Mild redness	Colder than right forearm	.....	.....	.....	Slight redness; colder than right forearm	.....
B. M.	25	Tingling	Slight redness	Paling	Tense paling of flexor surface at water line	.....	.....	.....
Control man, aged 28	25	.....	.....	Mild redness	Slight redness	.....	.....	.....
R. G.	24	Numb	Paling; tense paling at water line	5 itching red papules	Warm as right forearm	Warmer than right forearm	Subsiding	.....
Control man, aged 42	24	.....	Slight redness	.....	Colder than right forearm	Slight redness	.....	.....
T. R.	25	Tingling; paling; 3 itchy red papules	Itching	Warm as right forearm	.....	Subsiding	.....	.....
Control man, aged 31	25	.....	Slight redness	Colder than right forearm	.....	.....	.....	.....
J. M.	24	Goose skin; paling	Drawing	.....	Warm as right forearm	Burning of flexor surface of elbow	.....	.....
Control man, aged 24	24	.....	.....	.....	Colder than right forearm	.....	.....	.....
J. L.	25	Tingling; burning	Fine red itchy papules	Purpura†; paling	Dryness	.....	.....	.....
Control girl, aged 16	25	.....	Mild redness	.....	.....	.....	.....	.....
B. C.	23	Mild redness	Paling	Red papules; itching	Warmer than right forearm	Paling	Dryness	.....
Control girl, aged 12	25	Slight redness	.....	.....	Colder than right forearm	.....	.....	.....

* These tests were performed during the months of November and December, 1949.

In many of the cases in table 1, wool fat had been applied to an injury prior to the onset of the atopic eruptions. Adding suspicion to wool fat are 5 cases of winter eczema of the hands; all these patients were sensitive to the substance. The skin in infancy and childhood may be even more susceptible.

No inference is made that anybody should go dirty. Warm water is a cleansing agent for the skin that has no peer. Cutaneous secretions like sweat residues and portions of the lipid mantle are dissolved away with the minimum of irritation to the skin. In warm weather the skin can stand more bathing than in cold weather. The stress occasioned by the latter should cause a proportionate reduction in the amount of bathing. In warm weather the skin should be lightly covered, arms and legs; but in cold weather, the covering should be increased. Consulting the family album on the baby pictures of our parents is a lesson par excellence in protecting the skin. A covered skin is spared many of the minor mechanical, thermal, physical and chemical injuries. Children playing outdoors in the summer are spared the trauma from insect bites and contacts with noxious plants.

Why persons with atopic dermatitis tend to get well or improve in the summer is apparent in figure 1. Daily temperatures and humidities that stay above 52 place a subthreshold stress on their peripheral vascular systems. Why these persons improve or get well in the hospital is also apparent. Bed clothing stabilizes the ambient air around their skin and keeps the humidity high by delaying the evaporation of insensible sweating. J. S. (case 2, table 1) was so managed almost three years. He has not lost a day of work. Dropping temperatures and humidities were his signal to wear long underwear. Most of these patients had had food elimination therapies. J. M. (case 10, table 1) had lost 15 pounds (6.8 Kg.) from diet restriction which had not improved her symptoms or signs. B. C. (case 12, table 1) had not had eggs in two years nor any milk in three years. This food restriction did not prevent seasonal attacks. She wore union suits and prompt improvement resulted. At room temperature of 25.5 C., the same thermometer, slipped up her arm so that the bulb rested at the antecubital space, registered 36.5 C. (97.7 F.). This illustrates how clothing shields the skin from sudden changes in temperature and thereby stabilizes the ambient air and humidity. S. B. (case 4, table 1) had taken weekly "shots" for two years with no improvement or prevention of attacks. No food restrictions were imposed, and no formula changes were considered necessary. D. P. (case 13, table 1) was hospitalized 10 days. The formula was not changed. On the fifth day his crib was wrapped with cotton blankets, and the nozzle of a humidifier was placed at the foot. This procedure produced an environment corresponding

to that of July. A remarkable improvement occurred; symptoms vanished. The child went home five days later. The parents were instructed to keep the house humidity high. The method of stabilizing the air temperature and humidity is shown in figure 2. This patient, P. M. (case 3, table 1) has been kept relatively free of attacks for three years. In the summer he wears long-sleeved shirts and long pants, but with the onset of cool weather he dons, in addition, long underwear. During the fall of 1947 it suddenly turned cold and dry, and in the following

Fig. 2 (case 3).—Method of shielding the skin against sudden changes of environmental temperature. The mantle of cotton material delays evaporation of insensible sweat and thus keeps the skin in higher humidity ranges. The gloves were put on to illustrate the ease of shielding the skin of the body completely except for the face and neck.

week 15 patients with subthreshold atopic dermatitis were seen with symptoms and signs. Adequate clothing to meet the demands of weather is the basis of skin hygiene. Topical therapy consisted of placebos, roentgen rays and bentonite, with and without glycerin and olive oil. The marked cutaneous cooling from evaporation of sweat or moisture is illustrated by the patients with atopic dermatitis who have lesions around

the mouth and eyes and on the hands. In cold weather, it is necessary to avoid smearing the perioral skin with food and to keep the child indoors until the skin is dry. Tears wet the skin too. The lesions on the hands respond to the wearing of gloves, and, very important, the child must stop playing with soap and water. Often in the severe cases, bathing with water must be stopped until the skin improves.

SUMMARY

The prevention of atopic dermatitis could be the first achievement of the proposed [8] Council on Dermatologic Hygiene and Therapeutics.

RESPIRATION OF FULL TERM AND OF PREMATURE INFANTS

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ALTHOUGH numerous attempts to measure ventilation in early infancy have been reported since that of Eckerlein in 1890,[1] reasonable accuracy was not obtained until the body plethysmograph technic[2] was introduced. While this eliminated the dead space error of the mask technic, it introduced the difficulty of sealing the apparatus around the infant's neck without unphysiological pressure. Cross[3] avoided this by allowing the infant's face to protrude through a head piece of inflatable rubber and connected the recording spirometer to a specially designed integrator.[4] The first innovation allowed prompter relaxation by the infant and achieved greater freedom from leaks; the latter greatly reduced the labor of record analysis. In the present investigation we used a plethysmograph sealed at the neck but improved both in this regard and in its recording apparatus. These features, plus the additional data secured, are considered worth reporting.

METHODS

The apparatus used was a cylindrical chamber (65 cm. in length, 35 cm. in diameter and of 65 liter capacity) designed after the model of Murphy and

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From the Department of Pediatrics, Harvard Medical School and the Laboratory for Research on the Newborn, Boston Lying-in Hospital.

1. Eckerlein: Zur Kenntniss des Athmungsmechanismus der Neugeborenen, Ztschr. f. Geburtsh. u. Gynäk. **19**:120, 1890.

2. (*a*) Shaw, L. A., and Hopkins, F. R.: Respiration of Premature Infants, Am. J. Dis. Child. **42**:335 (Aug.) 1931. (*b*) Murphy, D. P., and Thorpe, E. S.: Breathing Measurements on Normal Newborn Infants, J. Clin. Investigation **10**: 545, 1931.

3. Cross, K. W.: Plethysmograph for Studying Respiration in the Newborn Infant, J. Physiol. **108**:37P, 1949.

4. Roberts, P. W., and Widdas, W. F.: Automatic Integrator for Volume Recorders, J. Physiol. **108**:37P, 1949.

Thorpe.[2b] A new feature was the neck piece[5] of inflatable rubber, to the inner surface of which a fine latex sleeve was attached so as to converge within the plethysmograph around the infant's neck. The inflated portion supplied rigidity, and the sleeve prevented leaks (fig. 1). This system was found to be leak proof (as tested by a weighted Krogh spirometer) and yet not the cause of undue pressure, as indicated by absence of venous obstruction, satisfactory skin color of the head and quality of breathing. Slight movement of the whole diaphragm assembly occurred on respiration but was not sufficient to alter stability or affect the linearity of the results obtained by calibration over the required range. Nevertheless, a method to reduce this movement further is being sought.

The recording apparatus was devised by Drs. Alvin Cahan, assistant in medicine at the Beth Israel Hospital, and Arthur Miller, of the Sanborn Company. It consisted of a semirigid tube connecting the interior of the plethysmograph to a

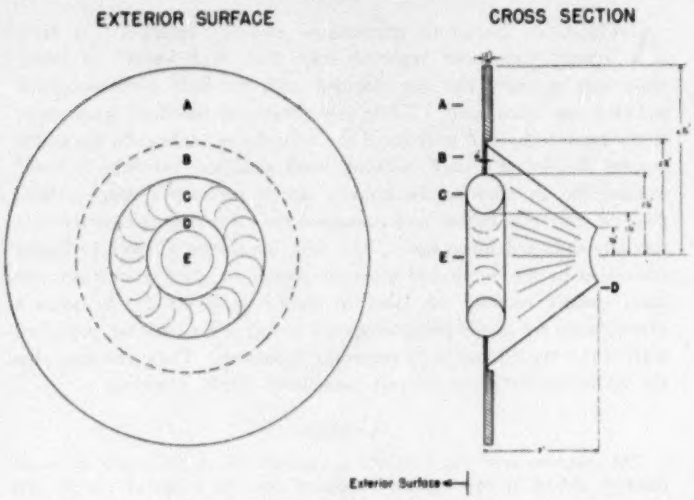

Fig. 1.—Construction of rubber neck piece for plethysmograph: *A*, firm rubber 7/32 inches thick to be clamped to the edge of the aperture; *B*, rubber 1/16 inch thick to allow stretching for passage of infant's head; *C*, inflatable rubber ring to fill space around infant's neck; *D*, thin latex sleeve to prevent leaks.

shallow metal cylinder 4 cm. in diameter covered by a rubber membrane. This was displaced by the pressure changes within the plethysmograph resulting from the infant's breathing. A small mirror attached eccentrically to the outer surface of this membrane reflected two parallel beams of light, triangular in cross section, from a fixed source, on two photoelectric tubes. As the infant's respiratory movements produced distortion of the membrane, the resultant movement of the reflected light beams caused a larger area of light to fall on one cell and a smaller area on the other, thus inducing changes of electric potential in the tube circuit. These

5. This neck piece was manufactured by the Davol Rubber Company, Providence, R. I.

were fed into a Sanborn Viso-Cardiette so that an upward movement of the stylus occurred when the pressure within the plethysmograph was raised (inspiration) and a downward movement when the pressure was lowered (expiration). The size of the record deflection could be altered at will by a simple adjustment on the Viso-Cardiette.

Calibration of the empty plethysmograph by rhythmical introduction of measured air volumes from 24 to 50 times a minute indicated a linear relation between the amount of air introduced and the movement recorded by the cardiette. With proper tension of the mirror-carrying diaphragm and suitable rigidity of the neck piece, linearity resulted from introduction of volumes up to 90 cc. (fig. 2). An attempt was then made to simulate the effect of the infant's volume with liter bottles, but this procedure was later abandoned and calibration for each infant was done with the infant in the plethysmograph. Amounts of 10, 20, 30, 40 and

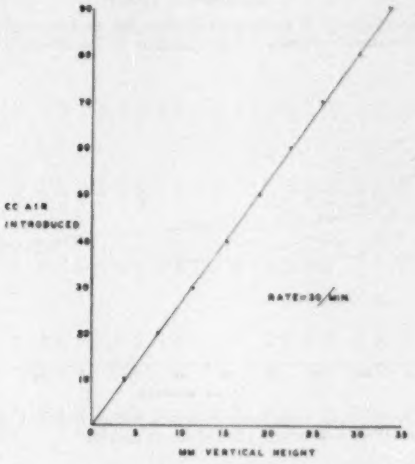

Fig. 2.—Relation of excursion of Cardiette stylus (abscissas) to amount of air introduced into plethysmograph (ordinates); calibration without infant in plethysmograph.

50 cc., respectively, of air were introduced at the beginning of a regular inspiration and usually withdrawn before the end of the subsequent expiration. This procedure was repeated three times for each volume and the mean increment of vertical deflection determined for the corresponding volume. The method had its obvious difficulties, particularly when respiration was periodic or rapid; in these circumstances the scatter of individual calibration readings about the mean was disturbingly wide. Nevertheless, since the means were satisfactorily linear (fig. 3), adequate calibration data were presumably obtained.

Only recordings made during well established sleep were used for the data to be presented below. The importance of providing sufficient time after placement in the plethysmograph for the respiration to reach basal values is illustrated in figure 4, which shows a steady decline in minute volume during sleep. The time

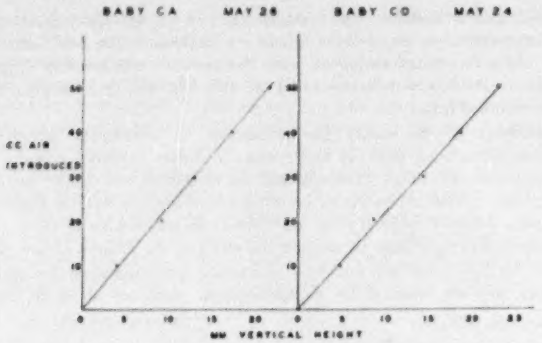

Fig. 3.—Two examples of calibration of recorded excursion of Cardiette stylus (abscissas) to measured volumes of air (ordinates) introduced without infant in plethysmograph.

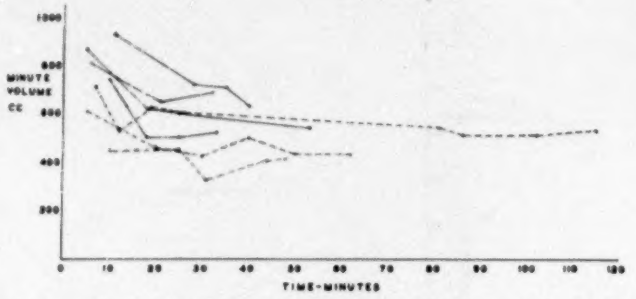

Fig. 4.—Effect of sleep (beginning at 0) on minute volumes of four full term (solid lines) and three premature (dotted lines) infants.

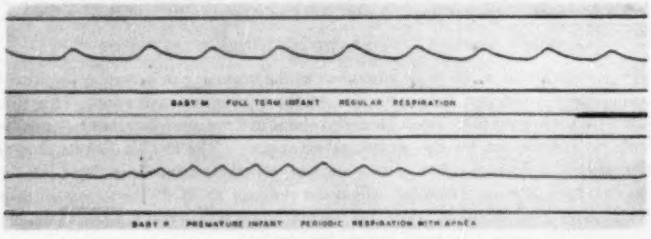

Fig. 5. —Upper curve: Cardiette tracing of respiration of full term infant: lower curve: tracing of respiration of premature infant, showing apnea before and and after a periodic cycle of respiratory activity. The duration of each record was 22 seconds.

TABLE 1.—*Breathing of Full Term Infants Observed May to August 1949*

Case No.	Name	Sex	Age, Hr.	Wt., Kg.	Surface Area, Sq. M.	Minute Volume			Tidal Volume			Rate	Character	Observations
						Cc.	Cc./Kg.	Cc./Sq.M.	Cc.	Cc./Kg.	Cc./Sq.M.			
1	B. Y.	M	72	3.20	0.215	544	170	2,530	13.3	4.16	61.8	41	Irregular	4 over 40 min.
2	H.	F	4	3.86	0.244	581	151	2,373	16.6	4.30	68.0	35	Regular	3 over 35 min.
3	L. A.	M	2½	3.52	0.227	511	145	2,247	17.0	4.83	75.0	30	Regular	3 over 15 min.
4	C. A.	M	15	3.81	0.235	668	175	2,843	18.6	4.88	79.2	36	Regular	3 over 13 min.
5	V.	M	34	3.64	0.230	798	223	3,469	13.3	3.66	57.9	60	Regular	2 over 5 min.
6	L. B.	M	4	2.78	0.193	629	226	3,290	17.0	6.12	88.1	37	Regular	1
7	C. B.	F	18	3.21	0.214	523	163	2,444	13.7	4.27	64.0	38	Regular	1
8	C. C.	M	17	3.24	0.212	635	196	2,995	16.2	5.00	76.4	39	Regular	1
9	G. A.	M	17	4.12	0.254	833	202	3,279	18.1	4.39	71.3	46	Regular	2 over 2 min.
10	M.	F	12	3.87	0.244	642	166	2,672	19.5	5.02	79.9	33	Regular	6 over 120 min.
11	C. D.	F	2	3.92	0.244	675	172	2,770	21.8	5.56	89.4	31	Regular and irregular	7 over 45 min.
12	T. A.	M	28	3.93	0.244	894	227	3,664	14.7	3.74	60.3	61	Irregular	3 over 7 min.
13	F.	M	34	3.73	0.235	746	200	3,174	20.2	5.42	86.0	37	Irregular	1
14	G. B.	F	11	3.36	0.219	710	212	3,242	13.9	4.14	63.5	51	Regular	4 over 14 min.
15	C. E.	F	2½	3.36	0.218	365	109	1,674	15.2	4.52	69.8	24	Periodic with apnea	4 over 50 min.
16	T. B.	M	14	3.07	0.205	630	209	3,073	15.8	5.15	77.2	40	Regular	2 over 10 min.
17	E.	M	8	3.45	0.221	527	153	2,385	21.1	6.12	96.5	25	Regular	3 over 25 min.
Average				3.53	0.227	642	182	2,810	16.8	4.76	74.3	39		
Standard Deviation								466				10.2		

TABLE 2.—*Data on Premature Infants Observed May to August 1949*

Case No.	Name	Sex	Gestation, Weeks	Age, Days	Weight, Kg.	Surface Area, Sq. M.	Minute Volume			Tidal Volume			Breathing		Observations
							Cc.	Cc./Kg.	Cc./Sq.M.	Cc.	Cc./Kg.	Cc./Sq.M.	Rate	Character	
1	F.	M	34	28	2.19	0.162	395	180	2,436	14.6	6.66	90.1	27	Periodic, mild	1
2	T. A.	F	35	7	2.07	0.158	389	188	2,889	11.1	5.41	70.3	35	Periodic	4 over 30 min.
3	L.	M	33	11	1.80	0.147	432	232	2,940	17.3	9.14	117.7	25	Periodic with apnea	4 over 30 min.
4	D. A.	F	36	12	1.93	0.153	428	222	2,797	11.3	5.86	73.9	38	Regular	1
5	P.	F	33	7	1.76	0.140	550	316	3,993	13.6	7.86	97.1	41	Periodic with apnea	4 over 30 min.
6	D. B.	F	37	3	2.05	0.156	409	200	2,622	11.4	5.56	73.1	36	Regular	1
7	D. B.	F	36	16	2.16	0.162	554	256	3,420	14.9	6.94	92.0	37	Periodic and regular	2
8	H.	M	30	41	1.70	0.137	390	231	2,839	9.4	5.53	68.6	42	Periodic	1
9	V. A.	F	36	6	2.07	0.158	581	281	3,677	16.1	7.78	101.9	36	Periodic and slow; regular	2 over 30 min.
10	V. B.	F	36⅛	4	2.07	0.158	403	196	2,535	12.6	6.09	79.4	32	Regular	1
11	V. B.	F	36⅛	7	2.04	0.158	396	194	2,506	8.4	4.27	53.1	47	Periodic	4 over 25 min.
12	C.	F	33	11	1.67	0.136	366	219	2,618	14.6	8.76	107.2	25	Periodic with apnea	6 over 40 min.
13	K.	M	39	5	2.13	0.163	409	192	2,509	13.6	6.48	83.5	30	Regular and periodic with apnea	6 over 77 min.
14	K.	M	39	6	2.13	0.163	449	211	2,755	17.3	8.12	106.1	26	Regular	5 over 40 min.
15	M. A.	M	33	8	1.55	0.131	286	184	2,176	12.4	8.00	94.8	23	Periodic with apnea	2 over 8 min.
16	M. A.	M	33	13	1.55	0.131	281	181	2,147	10.4	6.90	79.4	26	Periodic with apnea	2 over 6 min.
17	M. B.	F	33	14	1.56	0.133	381	241	2,865	13.1	8.42	98.5	29	Periodic with apnea; slow regular	5 over 50 min.
18	M. B.	F	33	21	1.82	0.143	542	296	3,790	14.6	7.85	102.0	37	Periodic with apnea	6 over 75 min.
19	B.	F	34	11	1.93	0.150	457	237	3,047	14.7	7.67	98.1	32	Periodic with apnea	5 over 50 min.
20	F. B.	M	34	4	1.82	0.146	355	194	2,418	12.2	6.70	83.6	29	Periodic and regular	9 over 140 min.
21	P. B.	M	34	4	1.82	0.146	450	247	3,082	11.0	6.00	75.4	41	Periodic and regular	8 over 160 min.
22	T. B.	F	35	3	2.04	0.156	477	234	3,058	13.3	6.42	85.4	36	Mostly regular; some periodic	12 over 60 min.
23	T. B.	F	35	5	2.04	0.156	552	271	3,589	17.3	8.48	110.9	32	Regular	2 over 4 min.
24	P.	M	35	6	2.04	0.154	386	190	2,519	14.4	7.11	93.6	27	Irregular	5 over 30 min.
Average					1.91	0.150	430	225	2,875	13.2	7.00	88.6	32.8		
Standard deviation									480				6.1		

required to reach a steady state varied somewhat, being 10 to 15 minutes of sleep for premature and about 20 minutes for full term infants. If an infant cried appreciably on entering the plethysmograph, the time required to reach a resting level seemed to be lengthened. Recordings were made over full minute intervals. Although only one 1-minute volume was accepted from certain infants, many records were taken from all. Those records accepted were taken only after the proper interval of sleep except in very few cases in which, with no crying and no awakening on insertion into the box, respiration was stabilized before the respective times chosen. Figure 5 shows examples of tracings from full term and premature infants. For the calculation of surface areas, Wetzel's grid,[6] based on weight and length, was employed.

The age of the 17 full term infants ranged from 2½ to 72 hours. Thirteen were observed in the first 24 hours. Since it seemed unwise to disturb premature infants soon after birth, the 17 prematures used for 24 observations were from eight hours to 42 days old, 20 being in the range from three to 16 days. The age range in the two groups thus necessarily presents certain differences.

TABLE 3.—*Comparative Data on Respiration of Full Term and of Premature Infants*

	Cc. Average (Max.-Min.)	Cc./Kg. Average (Max.-Min.)	Cc./Sq.M. Average (Max.-Min.)	Rate/Min. Average (Max.-Min.)
Tidal Volume				
17 Full term infants.....	16.8 (21.8-13.3)	4.70 (6.13-3.66)	74.3 (96.5-57.9)	39 (61-24)
24 Premature infants.....	13.3 (17.3- 8.4)	7.00 (9.14-4.37)	88.6 (117.7-53.1)	33.8 (47-22)
Minute Volume				
17 Full term infants.....	642 (894 - 365)	182 (267 - 100)	2819 (3664-1674)	.....
24 Premature infants.....	430 (561 - 281)	225 (318 - 180)	2875 (3998-2147)	.....

RESULTS

Table 1 contains the results from the full term infants, and table 2 the results from the prematures. In table 3 the data for the two groups are compared.

Minute Volume.—It will be noted that in relation to weight the results for prematures were 20 to 25 per cent higher than those for full term infants. However, when comparison is made on the basis of surface area, there was no significant difference between the average results of 2,875 and 2,819 cc., respectively, per square meter.

Rate.—It is surprising to find the respiratory rate of premature infants lower than that of full term infants. The standard deviation is much less in the former, and the results, when one considers the extra number observed, are possibly more trustworthy. The inclusion of two full term infants with the high respiratory rate of 60 possibly distorted the resultant average of the total 17. The average rate for the other 15 was 36 per minute, which is still above the average for the premature infants.

6. Wetzel, N. C.: The Baby Grid, J. Pediat. **29**:439, 1946.

Tidal Volume.—The average tidal volumes were 13.3 cc. for premature and 16.8 cc. for full term infants, or 88.6 and 74.3 cc. per square meter of body surface. The comparatively higher tidal volumes for premature infants might suggest a more efficient ventilation, but more data would be necessary to establish this conclusion.

Character of the Breathing.—Numerous patterns were recorded, sometimes changing from one to another as indicated in the following tabulation:

Character of Breathing	Full Term Infants	Premature Infants	Average Age from Conception, Weeks
Regular	12	5	37.4
Irregular	4	1	36.0
Periodic, without apnea *	..	4	37.1
Periodic, with apnea *	1	7	34.8
Regular, with intervals of periodicity	..	7	30.3
Total	17	24	....

* Apnea is defined as three or more seconds without breathing.

The marked tendency of premature infants toward periodic breathing must be noted. The large number with intervals of apnea may have accounted partly for the lower average rate in the premature infants. The tendency for periodic breathing with apnea to be associated with immaturity within the premature group will also be noted, although this relation is not statistically significant.

Effect of Age.—If the data for the premature infant group are analyzed, no tendency for minute volume, tidal volume or respiratory rate to change with age can be observed. A comparison of the two groups over the first days of life is not possible because of the age differences. In the full term infants, the minute volume tends to be moderately lower during the first 10 hours of life. This is a function of rate, since tidal exchange is fully comparable with the later periods. Nonetheless, further observations on the first 12 hours of life are called for, as in this period the major expansion of alveoli takes place.

Variations in the Same Infant from Day to Day.—On seven of the premature infants two observations each were undertaken, with intervals of from ½ day to 12 days separating the observations. It will be seen in table 2 in respect to minute volume that variations in either direction of up to 25 per cent can occur. These differences are exaggerated if rate and tidal volume are considered separately.

COMMENT

Observations reported in earlier publications [7] have been summarized in table 4. Figures for respiratory rate alone, appearing prior to 1890

7. (*a*) Dohrn, R.: Über die Grösse des respiratorischen Luftwechsels in den ersten Lebenstagen, Ztschr. f. Geburtsh. u. Gynäk. **32**:25, 1895. (*b*) von Reck-

(Footnote continued on page 762)

TABLE 4.—*Published Data on Volume and Rate of Neonatal Respiration*

Name	Date	Observations and Method	Minute Volume: Average, Cc.	Minute Volume: Average, Cc./Kg.	Average Rate	Tidal Volume: Average, Cc.	Tidal Volume: Average, Cc./Kg.	Character
Eckerlein [1]	1890	40 1-minute samples on 4 infants a day 1-10 days; mask to small spirometer; rebreathing	1,700	557*	51	35	11.6*	Noted periodicity and also Cheyne-Stokes respiration in 1 premature observed
Dohrn [7a]	1895	100 newborn (85 full-term, 15 premature) observed 5 minutes a day for 10 days; mask, tubing and valves to spirometer used	2,437*	...	62	39.3	.....	.....
Von Recklinghausen [7b]	1896	29 samples from 4 infants; 3 examined on two separate occasions	1,326*	425*	64	21.0	6.7*	Not stated
Gregor [7c]	1902	Apparently several observations on 1 infant; other recordings outside the neonatal period	1,283	393	58	23	6.9*	Not stated
Eckstein and Rominger [7d]	1901	Mask with local valves; only 7 infants aged 6 weeks or less, of which 2 were premature and 1 sick	.....	351	..	..	.....	Noted periodicity in both prematures
Vogt [7e]	1909	34 infants up to 10 days; pneumogram	.....	...	36	..	.....	Not stated
Salmi and Vuori [7f]	1910	14 prematures; pneumogram	No quantitative measurements					Periodic breathing in 12 of 14
Peiper [7g]	1911	Prematures only; number of records not stated; pneumogram	No quantitative measurements					9 tracings illustrate periodic breathing, sobbing, sighing, gasping and apnea
Vormittag [7h]	1913	Pneumogram; 28 full term infants, 1 to 7 days	.....	...	35	..	.....	.....
Häihä and Salmi [7i]	1913	7 prematures; pneumogram	No quantitative measurements					All periodic
		All Body Plethysmograph						
Murphy and Thorpe [7j]	1921	50 infants; 3 ½-minute samples each record	721	220	43	16.7	5.22*	Stated that Cheyne-Stokes breathing is rare
Deming and Washburn [7j]	1925	27 infants aged from 20 hr. to 13 wk. Infants 0-7 days	1,078 626	289* ...	41 ..	27.3 ..	7.05*	Regular 60%; periodic approximately 30%; "cogwheel" approximately 10%
Deming and Hanner [7k]	1926	18 infants aged up to 10 days; 141 records	851	280	44	19.8	6.36*	25-30% periodic; about ½ with apnea; some "cogwheel," usually slow rate
Howard and Bauer [7l]	1940	10 infants	731	250*	46.5	16.5	.....	Periodic with apnea; noted this was ½ as common as in prematures
Cross [7m]	1940	New plethysmograph; 26 infants; many records; 10 infants observed more than once	569	170*	58.7	20.6	5.9 *	Not stated
Boutourline-Young and Smith	1950	17 infants	642	182	39.0	16.8	4.76	1 out of 17 periodic with periods of apnea
		Premature Infants						
Shaw and Hopkins [7n]	1931	Body plethysmograph; 20 records on 9 infants	606	434*	56	12.3	7.3 *	Not stated
Wilson, Long and Howard [7o]	1942	Body plethysmograph; 28 infants	No quantitative measurements					23 out of 28 breathed periodically
Boutourline-Young and Smith	1950	Body plethysmograph; 24 records on 17 infants	430	295	32.9	13.3	7.0	18 out of 24 breathed periodically, 7 with apnea

* These values were calculated by us from available data.

Results expressed in terms of square meters are available only from Murphy and Thorpe and present study. For minute volume: Murphy and Thorpe, 3,385 cc./sq.M.; present study, 2,819 cc./sq.M. for full term infants and 2,975 cc./sq.M. for premature infants. For tidal volume: Murphy and Thorpe, 78.4 cc./sq.M.; present study, 74.5 cc./sq.M. for full term infants and 88.7 cc./sq.M. for premature infants.

and with a few sundry observations since,[8] are collected in table 5. When results have not been so expressed, the liberty has been taken of converting them into cubic centimeters per kilogram of body weight or per square meter of body surface, though only one published article, that of Murphy and Thorpe,[2b] includes data required for the latter conversion.

It is seen that results obtained with masks have been high as compared with those obtained with other equipment. When simple pneumographs were used to measure rates of respiration, the results have approached those obtained with the body plethysmograph. With the use of the plethysmograph and large groups of infants, lower minute volumes, ranging between about 220 and 290 cc. per kilogram, have usually been recorded, as shown in table 4.

With more stringent criteria of rest, Cross [7m] has obtained the new low level expressed by him as 3.67 cc. per ounce (28 Gm.) of body

linghausen, H.: Über die Athmungsgrösse des Neugeborenen, Arch. f. d. ges. Physiol. **62**:451, 1896. (*c*) Gregor, K.: Untersuchungen über die Athmungsgrösse des Kindes, Arch. f. Physiol. (Physiol. Abt.) 1902, supp., p. 59. (*d*) Eckstein, A., and Rominger, E.: Beiträge zur Physiologie und Pathologie der Atmung: I. Die Atmung des Säuglings, Ztschr. f. Kinderh. **28**:1, 1921. (*e*) Vogt, H.: Die Atemzahl des gesunden Kindes, Monatsschr. f. Kinderh. **42**:460, 1929. (*f*) Salmi, T., and Vuori, E. E.: Untersuchungen über den Atmungstypus der Frühgeburten, Acta pædiat. **9**:432, 1930. (*g*) Peiper, A.: Der Zerfall des Atemzentrums, Monatsschr. f. Kinderh. **47**:189, 1930. (*h*) Vormittag, S.: Untersuchungen über die Atmung des Kindes: Atemzahl und Atemform des gesunden Kindes, ibid. **58**:249, 1933. (*i*) Räihä, C. E., and Salmi, T.: Über die periodische Atmung der Frühgeborenen, Acta pædiat. **15**:198, 1934. (*j*) Deming, J., and Washburn, A. H.: Respiration in Infancy: Method of Studying Rates, Volume and Character of Respiration, with Preliminary Report of Results, Am. J. Dis. Child. **49**:108 (June) 1935. (*k*) Deming, J., and Hanner, J. P.: Respiration in Infancy: Study of Rate, Volume and Character of Respiration in Healthy Infants During Neonatal Period, ibid. **51**:823 (April) 1936. (*l*) Howard, P. J., and Bauer, A. R.: Irregularities of Breathing in the Newborn Period, ibid. **77**: 592 (May) 1949. (*m*) Cross, K. W.: The Respiratory Rate and the Ventilation in the Newborn Baby, J. Physiol. **109**:459, 1949. (*n*) Wilson, J. L.; Long, S. B., and Howard, P.: Respiration of Premature Infants: Response to Variations of Oxygen and to Increased Carbon Dioxide in Inspired Air, Am. J. Dis. Child. **63**: 1080 (June) 1942. (*o*) Eckerlein.[1] (*p*) Murphy and Thorpe.[2b] (*q*) Shaw and Hopkins.[2a]

8. (*a*) Gorham: On the Respiration of Infants, London M. Gaz. 1838, p. 203; cited by von Vierodt, K.: Physiologie des Kindesalters, in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1877. (*b*) Quetelet, A.: Über den Menschen und die Entwicklung seiner Fähigkeiten, Stuttgart, 1838, p. 390; cited by von Vierordt. (*c*) Mignot, A. R.: Recherches sur les phénomènes et morbides de la circulation, de la calorité et de la respiration chez les nouveau-nés, Thesis, Paris, 1851. (*d*) Monti: Physikalische Untersuchungen der Brustorgane der Kinder, cited by von Vierordt. (*e*) Rennebaum, F.: Die Atmungscurve des neugeborenen Menschen, Jena, A. Neuenhahn, 1884. (*f*) Hishikawa, J.: Die Regulation der Atemfrequenz beim Neugeborenen und in den ersten Lebensjahren, Schweiz. med. Wchnschr. **53**:341, 1923. (*g*) Bauer, A. R.: Respiration in Newborn Infants, Am. J. Dis. Child. **60**:1342 (Dec.) 1940.

weight, which represents 129 cc. per kilogram. Our own average value of 182 cc. per kilogram, although relatively low, is well above Cross's figure. It is therefore of interest that Cross's published data, when expressed by the usual method of dividing average minute volume (589 cc.) by average weight (3.47 Kg.), yield a figure of 170 cc. per kilogram, as listed in table 4. The considerably lower figure mentioned above is, in our opinion, the result of too enthusiastic application of the statistical method to the analysis of physiological data. His analysis involved the drawing of a regression line through his plotted results and the calculation therefrom of 3.67 as representing the difference (in cubic centimeters of minute volume per ounce of body weight) between one weight and another over the range he has covered. Thus his minute volume per unit weight figures is given by the expression $\frac{MV \cdot X}{\text{weight}}$,

TABLE 5.—*Published Data on Rate (Alone) of Neonatal Respiration*

Author	Date	Observations and Methods	Rate/ Minute	Range	Reference and Comment
Gorham [84]	1838	Not stated	41	Not stated	Rate awake given as 56 per minute
Quetelet [85]	1838	Not stated	44	70-93	Cited by von Vierordt *
Mignot [86]	1851	Not stated	35	Not stated	Cited by von Vierordt *
Monti [84]	1879	Not stated	33.5	Not stated	Cited by von Vierordt *
Rennebaum [87]	1884	"Large" series of infants; tambour on epigastrium	46	Not stated	Pause between inspiration and expiration not noted; small tidal volume related to smaller energy of contraction of diaphragm; speed of expiration related to increased elasticity of thorax
Hishikawa [87]	1922	Not stated	..	78-88	Cited by Vormittag [78]; said to have tied the infants down by the legs
Bauer [88]	1940	Pneumograph	60	120-98	Record usually obtained when the infants were asleep

* Von Vierordt [84] cited several of these authors and mentioned the following without giving exact references: Alix, rate 37; Valleix, rate 30, and Vogel, rate 26.4. Von Vierordt gave the mean rate as 35 a minute.

where MV is the minute volume and X is the minute volume for zero weight obtained by projecting his regression line.

The use of a regression line is justifiable only if it is straight, and the evidence for such linearity, both from his data and from our own when minute volume is plotted against weight, does not seem sound. Moreover, if one ignores mathematical considerations, such a line, even if straight, must be cut off in the range of weight 0 to 2 pounds (0.9 Kg.), as extrauterine life cannot be sustained below a certain weight level. Our recalculation of Cross's very carefully secured data was, in any case, essential to their comparison with other data, similarly calculated, in table 4.

Periodic breathing in infancy has been observed and commented on many times, as is apparent in the last column of table 4. As one might expect, the more premature the infant, the greater is the incidence of extreme periodicity, although the relationship is not statistically signi-

ficant in this series. The phenomenon offers an obvious obstacle to precise statement of volume or rate of respiration per minute, and has necessitated selection of intervals for measurements which began and ended at the same phase of respiratory activity. It was observed in the present study, as well as in those by Deming and others,[7j, k] that while the respiratory rate during properly selected intervals is lower in periodic breathing with apnea than in regular breathing the average tidal volume is, perhaps necessarily, increased. This provides a partial explanation for rate and volume differences between the prematurely born and the full term infants.

That the average minute volume figures per unit of body surface for full term and for premature infants approximate each other as closely as 2,819 and 2,875 cc. is not surprising, since it is commonly believed that metabolism is more directly related to surface area than to weight and since metabolic differences between full term and premature infants are not great. Since Talbot, Sisson and Moriarty [9] found premature infants of less than 1,800 Gm. to have less heat production (and heavier premature infants to have more) than full term infants, we have plotted minute volume per square meter against weight in the present series, but no significant trend emerged. The lightest premature had, however, easily the lowest minute volume per square meter.

Comparisons with the minute volumes of adults are of some interest. Their ventilation per square meter of body surface is, roughly, 3,500 cc.[10] The heat production of the average man is 35 to 40 calories per square meter per hour,[10b] which gives a reasonable average of about 37 calories per square meter per hour to be compared with one of about 27 calories per square meter per hour in the newborn.[11] Thus the metabolic ratio of neonates to adults is 27 : 37. If a similar ratio holds for lung ventilation, one might expect the minute volume of infants to be $27/37 \times 3{,}500$ cc., or 2,560 cc., a result within about 10 per cent of that actually obtained.

The matter of effective tidal ventilation is also interesting. The usual tidal volume per square meter of body surface for the average adult is about 250 cc., whereas the comparable value for the infant is

9. Talbot, F.; Sisson, W. R., and Moriarty, M. E.: The Basal Metabolism of Prematurity: Metabolism Findings in 21 Premature Infants, Am. J. Dis. Child. **26**:29 (July) 1923.

10. (*a*) Soley, M. H., and Shock, N. W.: The Rate of Respiratory Adjustment to Postural Change, Am. J. Physiol. **130**:772, 1940. (*b*) Du Bois, E. F.: Basal Metabolism in Health and Disease, ed 3, Philadelphia, Lea & Febiger, 1936.

11. Benedict, F. G., and Talbot, F. B.: Metabolism and Growth from Birth to Puberty, Publication 302, Carnegie Institution of Washington, 1921. Talbot, Sisson and Moriarty.[9] Marsh, M. E., and Murlin, J. R.: Energy Metabolism of Premature and Undersized Infants, Am. J. Dis. Child. **30**:310 (Sept.) 1925.

less than 100 cc. Nevertheless, approximately the same end is reached, if the roughly similar arterial carbon dioxide tensions of infants and adults [12] may be accepted as significant. The greater respiratory rate in infants will augment the effective alveolar ventilation, but the relative proportion of dead space and residual air for adults and for infants tempts one to speculate. The question of dead space may be approached in the following way:

The effective alveolar ventilation (EAV) is obtained by the formula $EAV = (T\text{-}D)\ R$, where T is tidal exchange, D is dead space and R is rate per minute. Relating this to unit of surface area,

Adults' EAV/sq. M. $= (T\text{-}D)\ R = (250\text{-}100)\ 14 = 2{,}100$ cc.

It is known that the metabolism (per unit of surface area) of newborn infants is but 5/7 that of adults; thus the infant should require 5/7 of 2,100 cc., or 1,500 cc., of alveolar ventilation per square meter to achieve approximately the same arterial partial pressure of carbon dioxide. This assumes no essential differences in the respiratory quotient, ventilation-diffusion and blood flow relationships, or proportion of functional residual air, between adults and infants. These are questionable assumptions, but if they are allowed,

Full term infants' EAV/sq. M. $= (T\text{-}D)\ R = (75\text{-}D)\ 39 = 1{,}500$ cc.

D thus becomes 37 cc. per square meter of body surface, or a dead space of 8.5 cc. for a usual infant with surface area of 0.23 square meters. A similar equation for data from premature infants gives a dead space of 43 cc. per square meter of body surface, or 6.5 cc. for an infant of 0.15 square meter surface area.

By these calculations both tidal volume and dead space are considerably reduced per unit of surface area when compared with adults but their proportion to each other remain very much the same. Direct observations on dead space and residual air in newborn infants are called for.

In view of the well known biologic fact that small organisms breathe more rapidly than large ones, the average respiratory rate of 33 per minute for premature infants as compared with 39 for full term ones is difficult to understand, except as it may be a result of periodic breathing. It may also be partially accounted for by the difficulty of timing a function which was not regular, though every effort was made to use only samples reflecting truly average performance.

SUMMARY

Quantitative and qualitative measurements of respiration of 17 full term and 17 premature infants (seven of the latter being observed on

12. Reardon, H. S.; Graham, B. D.; Wilson, J. L.; Baumann, M. L.; Tsao, M. U., and Murayama, M.: Acid-Base Equilibrium and Oxygen, Hemoglobin and Hematocrit Levels in Premature Infants, Am. J. Dis. Child. **79**:372 (Feb.) 1950.

two separate occasions) were obtained by electric recording of pressure changes within a body plethysmograph in which the infants were allowed to reach a full resting status. For full term infants the average respiratory rate was 39 per minute and the average minute volume 182 cc. per kilogram of body weight and 2,819 cc. per square meter of body surface. For premature infants, the average rate was 32.8 per minute and the average minute volume 225 cc. per kilogram of weight and 2,875 cc. per square meter of surface.

The quantitative similarity of ventilation when related to surface area is apparent. If the normal minute volume of the adult (3,500 cc. per square meter) is corrected for the greater heat production of adults than of newborn infants, a rough figure of 2,560 cc. per square meter per minute is obtained. This is interestingly near the measured ventilation of both premature and full term infants.

Periodic breathing occurred in 75 per cent of premature infants, with definite apnea between periods of respiration in 29 per cent. The relatively low respiratory rate of 33 per minute in the total group of premature infants may be a result of this phenomenon.

Miss Ruth Cherry provided technical assistance in this study; Dr. Jane Worcester aided in the statistical evaluations, and Dr. James Whittenberger made various suggestions and criticisms.

MEDITERRANEAN ANEMIA IN CHILDREN OF NON-MEDITERRANEAN ANCESTRY

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COOLEY and Lee [1] in 1925 described a series of patients with anemia, splenomegaly and changes in the bones which made up a disease entity that became known as "Cooley's anemia," "Mediterranean anemia," "erythroblastic anemia" or "thalassemia." [1a]

Gradually, the term Mediterranean anemia has become most widely used to describe this condition, since the disease is primarily found in the offspring of families native to areas adjoining the Mediterranean Sea. Other important manifestations of the disease include its familial nature, the presence of "target cells," a blood picture which is hypochromic and microcytic, conspicuous variation in the size of the red cells and increased resistance of the erythrocytes in hypotonic sodium chloride solutions. However, certain variations have been observed in this disease picture, and it is the purpose of this communication to report a series of cases of major and minor forms of Mediterranean anemia occurring in children of non-Mediterranean ancestry.

REPORT OF CASES

FAMILY 1.—L. S., a 10 month old Chinese infant, first entered the University of California Hospital on Sept. 6, 1949 because of recurrent anemia of seven months' duration. She had weighed 4 pounds 15 ounces (2,240 Gm.) at birth and was considered normal until the age of 3 months, when the parents first noticed that she was "pale." At the age of 5 months the parents also noted moderate lethargy. At that time she weighed 11 pounds 3 ounces (5,080 Gm.). When she was examined by her physician, it was found that the spleen was palpable and that the edge of the liver was ½ inch (1.3 cm.) below the costal margin. The following month the liver had enlarged to approximately 1 inch (2.5 cm.) below the right costal margin, and the spleen was also further increased in size. Roentgenograms of the chest, skull and long bones were reported as being normal. A diagnosis of Mediterranean anemia was made and a transfusion of whole blood given. After

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1. Cooley, T. B., and Lee, P.: A Series of Cases of Splenomegaly in Children, with Anemia and Peculiar Bone Changes, J. Dis. Child. **30**:447 (Sept.) 1925.

1a. The forthcoming fourth edition of the "Standard Nomenclature of Disease" lists the entity as "hereditary leptocytosis."

a second transfusion at the age of 6 months, both the liver and the spleen were noted to be reduced in size. The laboratory data in April, 1949, as obtained by an outside laboratory, were as follows:

White blood cells numbered 15,170, with 193 nucleated red cells per 100 white blood cells. The red cell count was 2,940,000. Hemoglobin measured 6.67 Gm. per 100 cc. The differential count on white blood cells was normal. The icterus index was 10 units. In the fragility test, beginning hemolysis for the patient was in 0.42 per cent and complete hemolysis in 0.30 per cent sodium chloride solution. For the control hemolysis began in 0.44 per cent and was complete in 0.32 per cent solution. The reticulocyte count was 8.2 per cent. There were pronounced anisocytosis, poikilocytosis, polychromasia and basophilic stippling of the red cells, and nucleated red cells were present in the peripheral blood. On May 23, 1949 the white blood cell count had increased to 31,720 (uncorrected for nucleated red blood cells).

The parents had noted that following each transfusion the baby had become more active, the color was better and there was a more vigorous appetite, but that in about four to six weeks the pallor returned as did the lassitude.

The patient was the only child of a 27 year old Chinese woman and a 37 year old Chinese man, both of whom were born in Canton Province, China. Neither they nor anyone in their family had ever been known to have any type of anemia. Both parents had been told that they had had mild tuberculosis as children, but repeated roentgenograms of the chest and physical examinations since then had revealed no signs of any activity. The mother had been entirely well during her pregnancy and had had an uncomplicated delivery. The past history and family history otherwise were essentially normal. The child had been born in Oakland, Calif., and had never been outside of that state.

Results of Physical Examination.—The child was pale but well nourished, with the facies of a normal Chinese infant. The cervical, axillary and inguinal nodes were barely palpable. The anterior fontanel measured ½ by ¼ inch (1.3 by 0.6 cm.). There was a slight hemic murmur over the entire precordium. The spleen was palpable about ½ inch below the left costal margin, and the liver was enlarged down to ½ inch below the right costal margin. A mongoloid spot was present over the lower part of the back. The results of the remainder of the physical examination were within normal limits.

Laboratory Data.—On Sept. 6, 1949 the hemoglobin concentration was 6.9 Gm., the red blood cell count 2,800,000 and the white blood cell count 17,400, with a normal differential count. There were 15 nucleated red blood cells per 100 white blood cells. The red blood cells showed marked anisocytosis, hypochromia, poikilocytosis and polychromasia. A few target cells were present. The packed cell volume was 19 cc. per cent, and the icterus index was 23. The red cell fragility test on venous blood showed initial hemolysis for the patient in 0.44 per cent and complete hemolysis in 0.28 per cent saline solution. Initial hemolysis for the control was in 0.44 per cent and complete hemolysis in 0.34 per cent sodium chloride solution. A fragility test on finger blood (by the method recommended by Dr. Carl Smith) revealed initial hemolysis in 0.40 per cent solution, with some unhemolyzed cells remaining in distilled water. The control showed initial hemolysis at 0.45 per cent and complete hemolysis at 0.325 per cent. Examination of bone marrow aspirated from the iliac crest disclosed hyperactivity of the red cell series. The patient had negative reactions to the Kolmer, Kahn, tuberculin and Schick tests.

Both parents were studied, and their laboratory data were as follows: The father had a hemoglobin concentration of 14.3 Gm. The red blood cell count was 7,520,000. Packed cell volume was 46 cc. per cent. The smear disclosed slight hypochromia, slight anisocytosis and slight poikilocytosis, while some of the cells showed basophilic stippling. There were a few target cells. The red cell fragility test for the father's blood showed initial hemolysis in 0.42 per cent and complete hemolysis in 0.28 per cent solution, while the control had initial hemolysis in 0.44 per cent and complete hemolysis in 0.34 per cent sodium chloride solution. The mean corpuscular volume was 61 cubic microns, the mean corpuscular hemoglobin 19 micromicrograms and mean corpuscular hemoglobin concentration 31 per cent. By the microfragility method initial hemolysis occurred at 0.40 per cent and was complete in 0.20 per cent, while for the control hemolysis began in 0.45 per cent and was complete in 0.325 per cent sodium chloride solution.

The mother had a hemoglobin concentration of 14.6 Gm. The red blood cell count was 7,540,000, and the packed red cell volume was 47 cc. per cent. The smear showed slight hypochromia, slight poikilocytosis and slight anisocytosis. There were microcytic cells and a few target cells, but only a rare cell displayed basophilic stippling. The red cell fragility test revealed initial hemolysis in 0.40 per cent and complete hemolysis in 0.26 per cent sodium chloride solution, the control having initial hemolysis in 0.44 per cent and complete hemolysis in 0.34 per cent solution. The mean corpuscular volume was 62 cubic microns, the mean corpuscular hemoglobin 19 micromicrograms and the mean corpuscular hemoglobin concentration 31 per cent. By the microfragility method initial hemolysis occurred at 0.40 per cent and was complete at 0.25 per cent, while the control began at 0.45 per cent and was complete at 0.325 per cent.

The patient received two transfusions of 150 cc. each, and at the time of her discharge from the hospital the hemoglobin concentration was 12.5 Gm.

Summary.—A 10 month old Chinese girl had anemia and hepatosplenomegaly, with the red blood cells showing pronounced anisocytosis, hypochromia, poikilocytosis and polychromasia. There was decreased fragility of the red blood cells in hypotonic sodium chloride solutions. Erythroblastosis was present. The parents had been born near Canton, China. They both had red blood cell counts over 7,500,000, with normal hemoglobin levels and packed cell volumes, and their red blood cells also showed hypochromia, anisocytosis, poikilocytosis and decreased fragility in hypotonic saline solutions. Basophilic stippling and target cells were present.

Family 2.—B. L. was born in the University of California Hospital on Feb. 13, 1945. She was the first child of a 17 year old white American woman of French extraction and of a 34 year old Filipino who had been born in the Philippine Islands. The pregnancy had been uneventful, and the child was entirely normal at birth and during the neonatal period. She was followed in the Well Baby Clinic of this hospital, and her development during the first year was normal. However, the gain in weight was not entirely satisfactory, since she had weighed 5 pounds, 4 ounces (2,381 Gm.) at birth and at 1 year of age weighed only 16 pounds 6 ounces (7,428 Gm.). The only illnesses had been an occasional infection of the upper respiratory tract.

In September 1947 she was seen in the Clinic because of an infection of the upper respiratory tract, and at that time her hemoglobin concentration was found to be 11.3 Gm., with 6,080,000 red blood cells and 17,850 white blood cells. The differential count of the white blood cells was normal, but the red cells showed slight anisocytosis and poikilocytosis. Despite the institution of adequate treatment

for the infection of the upper respiratory tract and the administration of ferrous sulfate by mouth, the hemoglobin level dropped to 10 Gm., although the red blood cell count consistently remained between 5,500,000 and 6,000,000 per cubic millimeter. She was first seen in the Pediatric Blood Clinic on Feb. 25, 1948, and at that time it was noticed that the red blood cells displayed anisocytosis, poikilocytosis and basophilic stippling. On that date, the red blood cell count was 5,900,000 and the hemoglobin content was 10.7 Gm. A fragility test showed beginning hemolysis in 0.41 per cent, with complete hemolysis in 0.20 saline solution. The reactions to the tuberculin, Schick and Wassermann tests were negative. Two months later the fragility test showed beginning hemolysis in 0.4 per cent with complete hemolysis in 0.2 per cent saline solution, while the control had beginning hemolysis in 0.4 per cent and complete hemolysis in 0.325 per cent solution. She has been followed in the Clinic for the past year and a half and continues to show a hypochromic, microcytic blood picture, in spite of the absence of any apparent infection and the administration of adequate doses of an iron preparation by mouth. On several occasions moderate numbers of target cells have been noted, as well as prominent basophilic stippling. At no time has the spleen or liver been enlarged, and the only enlargement of lymph nodes was one attributable to the infection of the upper respiratory tract.

The father was checked, and his red cell fragility test showed beginning hemolysis at 0.35 per cent, with complete hemolysis at 0.20 per cent, while the control showed beginning hemolysis at 0.45 per cent and complete hemolysis at 0.325 per cent. The father's packed cell volume was .52 cc. per cent, with 13 Gm. of hemoglobin per 100 cc. and 5,370,000 red blood cells per cubic millimeter. The mother's red cell fragility and complete blood count have been normal on repeated testing.

The patient had a tonsillectomy in December 1948, and immediately following this a hemorrhage from the tonsillar fossa occurred, with a drop of the hemoglobin level to 8 Gm. and a drop of the red cell count to 3,750,000. However, a subsequent rise of the hemoglobin content to 11 Gm. and of the red cell count to 5,600,000 took place with administration of an iron preparation alone.

L. L., a younger sister, was born in the University of California Hospital on Jan. 14, 1947, following an uneventful pregnancy. She weighed 6 pounds 10 ounces (3,005 Gm.). Her early course was entirely normal, except for an occasional infection of the upper respiratory tract which responded well to treatment, but in April 1948 she was studied because of the presumptive diagnosis of Mediterranean anemia made for her older sibling. At that time the results of the physical examination were entirely within normal limits. The liver and spleen were not enlarged, and the mother reported that no abnormality referable to anemia had been noted. The child's hemoglobin level was 10.7 Gm., with 6,500,000 red cells. The white blood cell count was 10,100, with a normal differential count. There were anisocytosis and poikilocytosis of the red blood cells, but no target cells or basophilic stippling were seen. The fragility test showed beginning hemolysis in 0.40 per cent solution, with complete hemolysis in 0.20 per cent, while the control showed beginning hemolysis at 0.45 per cent and complete hemolysis at 0.325 per cent. As part of the diagnostic work-up she was given adequate amounts of ferrous sulfate by mouth, but after six months there was no appreciable change in either the red blood cell count or the hemoglobin concentration. However, a rare target cell could now be seen in the peripheral blood smear. She has continued to be entirely well, although a hypochromic, microcytic blood picture is still present.

The third child, S. L., was born at the University of California Hospital on Sept. 3, 1948, following an uneventful pregnancy. She weighed 6 pounds 11

ounces (3.033 Gm.) at birth. Because of the findings in the other siblings she was checked in February 1949 and was observed to have a hemoglobin concentration of 9.5 Gm., a red blood cell count of 5,470,000 and a white blood cell count of 8,500, with a normal differential count. There was pronounced hypochromia, and many target cells were present. She was given ferrous sulfate by mouth, but four months later the hemoglobin level was still only 9 Gm., with 6,200,000 red cells. A fragility test in April 1949 revealed beginning hemolysis at 0.325 and complete hemolysis at 0.20 per cent, while the control showed beginning hemolysis at 0.40 per cent and complete hemolysis at 0.30 per cent. The child's progress has been normal, and she is being followed regularly in the Well Baby Clinic.

Summary.—Three children in one family had mild hypochromic, microcytic anemia which did not respond to iron medication. Their red blood cells showed anisocytosis, poikilocytosis, basophilic stippling and decreased fragility in hypotonic sodium chloride solutions. The mother was of French ancestry, and her blood values were entirely normal; but the father, a Filippino who had been born in the Philippine Islands, had decreased fragility of his red blood cells in hypotonic sodium chloride solution.

FAMILY 3.—D. R., a 14½ month old boy, was first seen at the University of California Hospital on Dec. 1, 1947 because of chronic anemia which had first been noted at the age of 2 months. After an uneventful pregnancy, he had been delivered at term with the aid of low forceps. The neonatal period was reportedly entirely normal, but on a routine check-up at the age of 2 months he was observed to be "very anemic" and received two transfusions of his father's blood. Up to this time there had been no noticeable jaundice, weakness, poorness of appetite or any other unusual symptom.

When he was 9 months old, he was again reported to be "very anemic," and another transfusion of whole blood was given. However, he still appeared entirely well to the parents and had not been ill except for mild infections of the upper respiratory tract. His appetite had continued to be good at all times.

He was the only child of a 24 year old Mexican man, who was well and had never had any known anemia, and of a 24 year old Mexican woman, who had "always been anemic" and had tired easily. The exact cause of the mother's anemia had never been determined, although she had received many types of medication, including treatment for a possible, but unproved, parasitic infestation. There was no other known familial history of anemia. The parents were unaware of any intermarriage in their ancestory with non-Mexicans.

The child's feeding history, vitamin intake and development had been within normal limits. On physical examination he was seen to be well developed and nourished and active and did not appear ill. His skin was clear, with no evident jaundice, and was of normal color. The heart and lungs were within normal limits. There was minimal beading of the costochondral junction. The liver was not enlarged, but the tip of the spleen was palpable. The results of the remainder of the physical examination were within normal limits.

Laboratory examination revealed a hemoglobin content of 9.9 Gm., a red blood cell count of 4,430,000 and a white blood cell count of 14,200, with an essentially normal differential count. The red cells exhibited moderate basophilic stippling, pronounced hypochromia, slight anisocytosis and polychromasia. A few target cells were present. The red cell fragility test showed beginning hemolysis at 0.45 per cent, with complete hemolysis at 0.30 per cent, while the control had beginning hemolysis in 0.45 per cent and complete hemolysis in 0.35 per cent sodium chloride solution.

The results of the father's red cell fragility test were as follows: Hemolysis began at 0.48 per cent, with complete hemolysis at 0.38 per cent. The control had beginning hemolysis at 0.44 per cent, with complete hemolysis at 0.36 per cent. The mother's red cell fragility test showed beginning hemolysis at 0.48 per cent, with complete hemolysis at 0.28 per cent. For the control beginning hemolysis was at 0.44 per cent, with complete hemolysis at 0.36 per cent. The mother's blood count revealed 4,160,000 red cells, with a hemoglobin concentration of 9 Gm. There were prominent hypochromia, anisocytosis and poikilocytosis of the red cells. The white blood cell count was 11,700, with a normal differential count except for eosinophilia (10 per cent).

Summary.—The red blood cells of a 14 month old Mexican boy with slight anemia and splenomegaly showed basophilic stippling, hypochromia, anisocytosis, polychromasia, target cells and increased resistance in hypotonic sodium chloride solution. Both parents were Mexican, and the mother, who had an unexplained anemia of many years' duration, also was demonstrated to have mild hypochromic, microcytic anemia, with red blood cells that exhibited hypochromia, anisocytosis, poikilocytosis and decreased fragility in hypotonic sodium chloride solutions.

FAMILY 4.—The hospital records revealed that D. P., a 17 month old child, was first seen in the University of California Hospital on Oct. 15, 1942, because of anemia that had been present since the first two months of life. She had been born in a full term, normal delivery and weighed 6 pounds (2,722 Gm.) at birth. No jaundice or other abnormality was noted at the time of birth. She was breast fed for one week, and then an evaporated milk formula was added as a supplement. The gain in weight was poor during the first month of life, and prior to the age of 3 months it was noted that the child was definitely pale. At the age of 5 months she was seen by a physician who discovered severe anemia and gave the child a transfusion. The child was then seen in Los Angeles, where several blood and roentgenographic studies were performed, and the parents were told that the child had "either Mediterranean anemia or von Jaksch's anemia." Again transfusions were given, and they were continued at three to four week intervals to the time of her entry to this hospital.

The parents reported that when the child was in need of a transfusion she became restless, perspired freely, urinated frequently and had a slight fever. The "stomach and spleen" increased enormously in size at this time. There were also anorexia, some regurgitation and absolute refusal of foods and milk for appreciable periods. Respiration became rapid and labored, and there were alternating periods of constipation and diarrhea. After transfusions, the baby ate better, gained weight, did not perspire, slept better and urinated less frequently. Both parents were Chinese, the father having been born in Canton Province, China, and the mother in Fresno, Calif. There was one brother, aged 3 years, who was living and well and had no evidence of a similar condition. No blood disease had been known to exist in any other member of the family. Adequate diet and vitamin supplements had been offered to the child, and the development had been within normal limits.

Physical examination revealed a small, underdeveloped, irritable child of obvious Chinese ancestry, who was perspiring freely, particularly over the head. A few lymph nodes were palpable in the right cervical area, but other lymph nodes were not enlarged. The skin had poor turgor and deficient subcutaneous tissue. It was described as being greenish yellow. A large bluish mongolian spot was present over the lower part of the back and sacrum. The anterior fontanel was approximately 3 cm. in diameter, and there was noticeable bossing of parietal and occipital bones. Eight teeth were present. The conjunctivas

were slightly icteric. The thorax showed beading of the costochondral junctions. The heart was enlarged, and a hemic murmur was heard over the entire precordium. Diastasis recti abdominis and a small umbilical hernia were present. The spleen was large and firm and extended to the pelvic crest. A large notch was easily palpated. The liver was palpable 2 inches (5 cm.) below the right costal margin. There was questionable flaring of the epiphyses of the long bones. The impression on entry was that this child had "Mediterranean anemia" and had suffered from rickets and malnutrition.

Blood chemical tests revealed 11.2 mg. of calcium and 5.5 mg. of phosphorus per 100 cc. Phosphatase measured 4.4 Bodansky units and the carbon dioxide content 39 volumes per cent. There were 0.81 mg. of ascorbic acid, 4.01 Gm. of albumin, 3.8 Gm. of globulin and a total protein content of 7.8 Gm., per 100 cc. The blood count on her admission revealed a hemoglobin content of 3.7 Gm. per 100 cc., with 1,900,000 red blood cells and 49,100 nucleated cells per cubic milli-

Roentgenograms of Chinese girl, 17 months old, with Mediterranean anemia. *A* is of forearm, *B*, of the hand, and, *C*, of the foot. Dilatation of medullary cavities, osteoporosis, swelling of metacarpals and an apparent increase in trabeculation are present.

meter (corrected to 17,200 white blood cells with the elimination of the nucleated red blood cells). The reactions to the tuberculin and Kahn tests were negative. Roentgenograms showed diffuse enlargement of the heart. The long bones were reported to have lost their normal graceful curves and to have become more rectangular. The cortices were thinned, with severe osteoporosis and with wide trabecular spaces. These changes were evident in the radiuses, ulnas, humeri, metacarpals, femurs, tibias and fibulas and were considered to be characteristic of the osseous changes of "Cooley's Mediterranean anemia" (figure). No roentgenographic abnormality of the skull was present.

The parents and the siblings were examined but did not have any of the physical changes characteristic of Mediterranean anemia. The 3 year old sibling had 10.8 Gm. of hemoglobin per 100 cc., with 4,500,000 red blood cells and 14,000 white blood cells per cubic millimeter. The differential count was normal. How-

ever, the red blood cells showed polychromasia, anisocytosis and some microcytosis. The father's hemoglobin content was 13.7 Gm. per 100 cc., with 5,400,000 red blood cells and 8,300 white blood cells per cubic millimeter, and a normal differential count. No abnormal cells were noted in the smear. The mother's hemoglobin level was 13 Gm., with 5,500,000 red blood cells and 9,450 white blood cells. The differential count was normal except for eosinophilia (8 per cent). Again no abnormal cells were noted on the peripheral smear. Unfortunately, red blood cell fragility tests were not done on the parents or on the sibling.

The patient received several transfusions, and at the time of her discharge from the hospital the hemoglobin concentration was 13 Gm., with 4,800,000 red blood cells and 8,050 white blood cells. Twenty per cent of the nucleated cells were of the erythroid series.

The child reentered the hospital on Jan. 1, 1943. Three weeks before this entry the hemoglobin concentration had dropped to 3.7 Gm., and the child had been admitted to another hospital, where she had received a blood transfusion and six roentgen treatments to the spleen. "Liver shots" and a vitamin B preparation had also been given during the hospitalization.

Results of physical examination were essentially as they had been at the time of the first entry. The hemoglobin content was 6 Gm., with 2,550,000 red blood cells and 16,300 nucleated cells including 59 per cent neutrophils, 1 per cent eosinophils, 3 per cent basophils, 15 per cent lymphocytes, 3 per cent monocytes and 19 per cent nucleated red cells. Blood chemical studies showed 10.8 mg. of calcium and 5.6 mg. of phosphorus. Phosphatase was 6.1 Bodansky units. Albumin measured 4.9 Gm., globulin 3.3 Gm. and total protein 8.2 Gm., per 100 cc. The icterus index was 19.6. The red cell fragility test revealed starting hemolysis in 0.45 per cent and complete hemolysis in 0.30 sodium chloride solution. The baby's blood was group B type MN Rh positive. She received three transfusions, and at the time of her discharge the hemoglobin level was 10 Gm., with 3,900,000 red blood cells. Seventy-six per cent of the nucleated blood cells were of the erythroid series. In March 1943 she was hospitalized at Stanford University Hospital because the University of California Hospital was quarantined. The clinical impression of staff members there also was that this child had Cooley's Mediterranean anemia. The child was seen here on further occasions in 1943 because of the need for transfusions, but no other diagnostic studies were done.

Summary.—Another Chinese girl is reported on with anemia, hepatosplenomegaly, erythroblastosis in the peripheral blood and decreased fragility of the red blood cells in hypotonic sodium chloride solution. The characteristic roentgenographic changes of Mediterranean anemia were present in the bones. Of particular interest is the fact that the father of this patient also was born near Canton, China.

COMMENT

The severe form of Mediterranean anemia is a familial disease usually occurring in children of Mediterranean origin and is characterized by early onset of progressive anemia, pallor, splenomegaly, the development of a mongoloid facies and typical roentgenographic changes of the bones. The peripheral blood shows severe anemia which is hypochromic and microcytic. There is usually erythroblastosis, and the red cells display remarkable variation in size, as well as polychromatophilia and basophilic stippling. Target cells are almost always present. There is decreased

fragility of the red blood cells when tested with hypotonic sodium chloride solutions, and in some instances complete hemolysis does not occur, even in concentrations of saline solution as low as 0.20 per cent. The bone marrow shows an increase in the proportion of normoblasts to other nucleated cells.

Originally, it was believed that the disease was present only in the severe form, but in 1940 Dameshek,[2] Wintrobe, Mathews, Pollack and Dobyns [3] and, later, Strauss, Daland and Fox [4] independently described a milder form of the disease which was characterized by mild or absent anemia, increased reticulocytosis, absence of erythroblastosis and presence of anisocytosis, poikilocytosis, target cells and basophilic stippling of the red cells in the peripheral blood. In the mild form, too, there was decreased fragility of erythrocytes in hypotonic sodium chloride solutions. In some cases of the mild form of the disease the red blood cell count was higher than normal, even though the hemoglobin concentration and hematocrit reading were normal or reduced. It had been suggested by Caffey [5] that persons with mild Mediterranean anemia might reach adult life and constitute the source of transmission of the disease, and Angelini [6] and Caminopetros [7] had also proposed the existence of a genetic carrier.

The work of Dameshek, Wintrobe and his co-workers, Strauss and his associates and others [8] thus confirmed this hypothesis and further demonstrated that in cases of severe Mediterranean disease both parents will show some abnormality of the red cells. At present, it is believed that the disease is due to an anomaly of the red blood cell which is

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2. Dameshek, W.: "Target Cell" Anemia: Anerythroblastic Type of Cooley's Erythroblastic Anemia, Am. J. M. Sc. **200**:445-454 (Oct.) 1940.

3. Wintrobe, M. M.; Mathews, E.; Pollack, R., and Dobyns, B. M.: A Familial Hemopoietic Disorder in Italian Adolescents and Adults Resembling Mediterranean Disease (Thalassemia), J. A. M. A. **114**:1530-1538 (April 20) 1940.

4. Strauss, M. B.; Daland, G. A., and Fox, H. J.: Familial Microcytic Anemia: Observations of 6 Cases of a Blood Disorder in an Italian Family, Am. J. M. Sc. **201**:30-34 (Jan.) 1941.

5. Caffey, J.: Skeletal Changes in Chronic Hemolytic Anemias (Erythroblastic Anemia, Sickle Cell Anemia and Chronic Hemolytic Icterus), Am. J. Roentgenol. **37**:293-324 (March) 1937.

6. Angelini, V.: Primi risultati di ricerche ematologiche nei familiari di ammalati di anemia di Cooley, Minerva med. **2**:331-332 (Sept. 30) 1937.

7. Caminopetros, J.: Recherches sur l'anémie érythroblastique infantile, des peuples de la Méditerranée orientale: étude nosologique, Ann. de méd. **43**:27-61 (Jan.) 1938.

8. Smith, C. H.: Familial Blood Studies in Cases of Mediterranean (Cooley's) Anemia: Diagnosis of the Trait, or Mild Form of the Disease, Am. J. Dis. Child. **65**:681-701 (May) 1943.

inherited as an incomplete recessive[9] or incomplete dominant characteristic. In the person who is heterozygous, there usually is an absence of symptoms and the condition can be diagnosed only by a careful examination of the blood. However, when the anomaly is inherited from both parents, the homozygous person presents the manifestations of the serious disorder first described by Cooley and Lee and known as "Cooley's anemia" or "thalassemia major."

Although the disease in both its major and its minor forms is commonest in peoples from the area surrounding the Mediterranean Sea (especially Italy, Greece, Syria and Armenia), an increasing number of cases is being reported in non-Mediterraneans—in persons of Argentinean,[10] Chinese,[11] Egyptian,[12] English,[13] Filipino,[14] French,[15] German,[16] Indian,[17] Spanish[18] and Turkish[19] ancestry. Of interest is the report

9. Valentine, W. M., and Neel, J. V.: Hematologic and Genetic Study of the Transmission of Thalassemia (Cooley's Anemia; Mediterranean Anemia), Arch. Int. Med. **74**:185-196 (Sept.) 1944.

10. Caselli, E. G., and Sribman, I.: Anemia eritroblástica de Cooley (con presentación de un caso) reseña histórica y literatura pediátrica Argentina, Arch. argent. de pediat. **24**:187-196 (Sept.) 1945.

11. Foster, L. P.: Cooley's Syndrome (Erythroblastic Anemia) in a Chinese Child, Am. J. Dis. Child. **59**:828-834 (April) 1940. Gardner, L. B.: Cooley's Erythroblastic Anemia in 2 Chinese Boys, J. Pediat. **31**:347-354 (Sept.) 1947. Greenblatt, I. J.; Cohn, T. D., and Deutsch, H. L.: Mediterranean Target-Oval Cell Syndrome in an Adult Chinese Male: Report of a Case, Ann. Int. Med. **24**:259-261 (Feb.) 1946. Scott, A. V.: Cooley's Anemia (Mediterranean Anemia) in a Chinese Child, Chinese M. J. **65**:77-84 (March-April) 1947. Wang, C. Y., and Khoo, F. Y.: Hemolytic Anemia with Erythroblastaemia: Report of 3 Cases Seen in Chinese Infants, ibid. **58**:177-192 (Aug.) 1940.

12. Diwani, M.: Erythroblastic Anaemia with Bone Changes in Egyptian Children: Possible Cooley's Type, Arch. Dis. Childhood **19**:163-168 (Dec.) 1944.

13. Bywaters, E. G. L.: The Cooley Syndrome in an English Child, Arch. Dis. Childhood **13**:173-187 (June) 1938.

14. Slaten, E. F.: Familial Erythroblastic Anemia (Cooley's Anemia): Report of Possible Cases in 2 Filipino Brothers, Hawaii M. J. **7**:210-213 (Jan.-Feb.) 1948.

15. Olmer, J., and Sarles, H.: Remarques cliniques et étiologiques sur une érythroblastose de l'adulte, Bull. et mém. Soc. méd. d. hóp. de Paris **61**:293-294, 1945.

16. Freudenberg, E., and Esser, M.: Zur Pathogenese der Cooley-Anaemie, Ann. paediat. **158**:128-166, 1942.

17. (*a*) Chaudhuri, K. C.: Erythroblastic Anemia of Cooley, Indian J. Pediat. **14**:76-80 (April) 1947. (*b*) Coelho, G., cited by Chaudhuri.[17a] (*c*) Dhayagude, R. G.: Erythroblastic Anemia of Cooley (Familial Erythroblastic Anemia) in an Indian boy, Am. J. Dis. Child. **67**:290-293 (April) 1944. (*d*) Malhotra, R. P., and Chhuttani, P. N.: A Case of Cooley's Anemia, Indian M. Gaz. **79**:198-199 (May) 1944. (*e*) Mukherji, M.: Cooley's Anemia (Erythroblastic or Mediterranean Anemia), Indian J. Pediat. **5**:1-7 (Jan.) 1938. (*f*) Napier, L. E.; Shorten, J. A., and Das Gupta, C. R.: Cooley's Erythroblastic Anæmia, Indian M. Gaz.

of Caminopetros who studied the family trees of a large group of persons with Mediterranean anemia in eastern Greece and brought out the surprising fact that the ancestry of these Greeks included some Chinese who had migrated to Asia Minor. It has been suggested [20] that this might account for the "mongolian eye" noted in some cases. Wintrobe [21] has observed the adult form of the disorder in a family from Costa Rica who were descended from Scotch and Spanish persons, and it has also been reported [22] in two Bucharan Jews from the Caspian Sea region and in a 17 year old youth from South Africa.[23] Several cases have also been described in Negroes.[24]

Thus, we find that, even though Mediterranean anemia was first believed to be a severe childhood disease with a poor prognosis that was seen only in peoples from the Mediterranean area, it is actually a disease of adults, as well as of children, manifesting itself through a wide range of clinical severity—with some patients showing severe symptoms, others having a carrier state and still others, displaying mild forms, who may have no anemia and a normal life span. All these types are encountered in peoples from various parts of the world.

The cases herein reported illustrate further that Mediterranean anemia in both its major and its minor forms is not restricted to patients of Mediterranean origin.

74:660-664 (Nov.) 1939. (*g*) Patel, N. D., and Bhende, Y. M.: Erythroblastic Anemia with Kyphosis and Cirrhosis of Liver, Indian J. Pediat. **6**:217-222 (Oct.) 1939.

18. Jaso, E.; Alés Reinlein, J. M., and Pardo Urdapilleta, J.: El primer caso español de anemia de Cooley, Rev. clin. españ. **4**:425-429 (March 30) 1942. Sendrail, M.; Lyon, A., and Lasserre, J.: Infantilisme splénique de type Cooley, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:902-905 (June 8) 1936.

19. Saracoglu, K.: Cooleysche Anämie in der Türkei, Wein med. Wchnschr. **93**:217-221 (March 20) 1943.

20. Wolman, I. J., and Dickstein, B.: Changing Concepts of Mediterranean (Cooley's) Anemia, Am. J. M. Sc. **212**:723-737 (Dec.) 1946.

21. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1946.

22. Schieber, C. L.: Target-Cell Anemia: Two Cases in Bucharan Jews, Lancet **2**:851-852 (Dec. 29) 1945.

23. Altman, A.: Cooley's (Mediterranean) Anemia in a South African-Born European Adolescent, South African M. J. **20**:476-478 (Aug. 24) 1946.

24. Dameshek, W.: Familial Mediterranean Target-Oval Cell Syndromes, Am. J. M. Sc. **205**:643-660 (May) 1943. Faber, H. K., and Roth, B. M.: Mediterranean Anemia (Cooley) in a Negro Girl, J. Pediat. **28**:610-612 (May) 1946. Lubitz, J. M.: Target Cells and Other Abnormalities of Red Cells in Presence of Normal Erythrocyte Count and Hemoglobin Content, Am. J. Clin. Path. **15**:305-311 (Aug.) 1945. Schwartz, S. O., and Mason, J.: Mediterranean Anemia in the Negro: A Report of 4 Cases and Their Families, Blood **4**:706-721 (June) 1949. Stiles, M. H.; Marlove, C. H., and Dangerfield, C. D.: Mediterranean Anemia: Report of a Case in a Negro, Northwest Med. **45**:23-27 (Jan.) 1946.

SUMMARY

A series of cases of Mediterranean anemia in non-Mediterraneans who showed both the major and the minor manifestations of the disease is presented. The patients included Chinese, French-Filipino and Mexican children.

Summary of Hematological Findings in Families with Mediterranean Anemia

	Nationality	Anemia	Red Blood Cells*					Red Blood Cell Fragility
			Target Cells	Nucleated R. B. C.	Basophilic Stippling	Aniso-cytosis	Poikilo-cytosis	
Family 1								
Child L. S.		Hypochromic, micro-cytic	+++	++++	++	++++	++++	Decreased
Father	Chinese	Normal hemoglobin; high R. B.C. count	++	0	++	++	++	Decreased
Mother	Chinese	Normal hemoglobin; high R. B.C. count	++	0	+	++	++	Decreased
Family 2								
Child B. L.		Hypochromic, micro-cytic	++	0	++	++	++	Decreased
Child L. L.		Slightly low hemo-globin; high R. B. C. count	+	0	0	++	++	Decreased
Child S. L.		Slightly low hemo-globin; high R. B. C. count	+++	0	+	++	++	Decreased
Father	Filipino	0	+	0	+	0	0	Decreased
Mother	French	0	0	0	0	0	0	Normal
Family 3								
Child D. R.		Slightly hypochromic, microcytic	++	0	++	++	++	Decreased
Father	Mexican	0	0	0	0	0	0	Normal
Mother	Mexican	Slightly hypochromic, microcytic	+	0	+	++	++	Decreased
Family 4								
Child D. P.		Hypochromic, micro-cytic	++	++++	+	+++	++++	Decreased
Father	Chinese	0	0	0	0	0	0	?
Mother	Chinese	0	0	0	0	0	0	?

* Plus signs indicate presence and intensity of symptoms. Zeros indicate absence of symptoms.

ERYTHROBLASTOSIS FETALIS

VI. Prevention of Kernicterus

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IN PREVIOUS reports [1] we have shown that during a 12 year study period (1937 through 1948) kernicterus was the chief hazard to the recovery of liveborn infants with erythroblastosis fetalis seen at the Children's Medical Center, Boston, and the Boston Lying-in Hospital. Kernicterus not only has been the chief cause of death in liveborn infants but has led to brain damage in a small percentage of surviving infants, who present an important and tragic socioeconomic problem. We have summarized the evidence [2] which indicates that kernicterus is an acute condition of early postnatal life and have outlined the factors which are related to the likelihood of its occurrence in babies with erythroblastosis fetalis (high maternal titer, immaturity, male sex and previous occurrence in a family). We emphasized that maturity of the infant is an important

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1. (*a*) Vaughan, V. C., III; Allen, Fred H., Jr., and Diamond, L. K.: Erythroblastosis Fetalis: I. Problems in the Interpretation of Changing Mortality in Erythroblastosis Fetalis, Pediatrics **6**:173-182 (Aug.) 1950. (*b*) Allen, F. H., Jr.; Diamond, L. K., and Vaughan, V. C., III: Erythroblastosis Fetalis: II. Prognosis in Relation to History, Maternal Titer, and Length of Fetal Gestation, ibid., to be published. (*c*) Diamond, L. K.; Vaughan, V. C., III, and Allen, F. H., Jr.: Erythroblastosis Fetalis: III. Prognosis in Relation to Clinical and Serologic Manifestations at Birth, ibid., to be published.

2. Vaughan, V. C., III; Allen, F. H., Jr., and Diamond, L. D.: Erythroblastosis Fetalis: IV. Further Observations on Kernicterus, Pediatrics, to be published.

safeguard against the occurrence of kernicterus. It is the purpose of this paper to show that in a group of infants in whom immaturity has been intentionally avoided the liberal use of exchange transfusion has apparently been additionally responsible in part for the nearly complete disappearance of kernicterus as a complication of erythroblastosis fetalis. Data will be presented which indicate that there is a very close relation between kernicterus and jaundice.

The statistical data to be presented are derived from the study of 368 liveborn Rh-positive babies of sensitized Rh-negative mothers who were seen by us at the Children's Medical Center (Children's Hospital) between Jan. 1, 1947 and April 2, 1950 and at the Boston Lying-in Hospital and the Richardson House (private wards of the Boston Lying-in Hospital) between Jan. 1, 1945 and April 2, 1950. The data were coded and analyzed with the help of the McBee Keysort system. Information regarding certain details was lacking in some cases, and this has led to discrepancies in the totals among the various tables. However, it is unlikely that missing information invalidates in any way the conclusions to be drawn from the results given.

The cases observed at the Children's Hospital between Jan. 1, 1945 and Dec. 31, 1946 were omitted from the analysis because this group shows important differences with respect to sex, severity of disease and outcome from the rest of the cases. These differences have been demonstrated by Vaughn and co-workers [18] and preclude the inclusion of these cases in this analysis. Had they been included, the value of exchange transfusion would have appeared greater.

In the Children's Hospital material of 1947 to 1950, cases were omitted in which the baby was admitted to the hospital later than 24 hours after birth, since in these cases as a group the patients had severe disease and a high incidence of kernicterus and few of them were treated by exchange transfusion. Inclusion of these cases would have further increased the apparent benefit of exchange transfusion. Cases of babies who died during the first 24 hours of age were omitted because we have never seen kernicterus in such a baby but have reason to believe that in a quite large proportion of them clinical and pathological evidence of kernicterus would have developed if they had survived for another 48 hours; it is hardly right, therefore, to classify them under the heading "no kernicterus," while they certainly cannot be classified under the heading "kernicterus," and the only alternative was to omit them from the analysis. Cases of stillbirth were omitted except in tables 7 and 8; we have never seen kernicterus in a stillborn baby. Data on the cases omitted from the statistical analysis are presented in table 9. All the babies seen at the Boston Lying-in Hospital or the Richardson House were born there, except for a few of the stillbirths, and all the mothers were followed during pregnancy.

The analysis includes, therefore, only the cases of babies admitted before 24 hours of age and surviving more than 24 hours. The groups included in the analysis are comparable, year to year and hospital to hospital, with respect to the factors of sex, titer, maturity, past history and severity of disease at birth and form a representative group as far as the problems of erythroblastosis fetalis in newborn (liveborn) infants are concerned, except for the absence of that group of seriously ill infants who die despite treatment in the first few hours of life.

Those babies were considered to have been treated by exchange transfusion who received at least 150 cc. of donor blood in the process of doing the exchange. The highest antepartum Rh antibody titer in bovine albumin was taken as the maternal titer in each case. There has

TABLE 1.—*Changing Incidence of Kernicterus in Relation to Maturity and to Use of Exchange Transfusion*

	1945	1946	1947	1948	1949	1950
No kernicterus	15	31	75	80	100	29
Kernicterus	6	9	10	10	2	1
Per cent kernicterus	28.6	22.5	11.8	11.1	2.0	3.3
No induction of labor or section*	13	13	41	47	60	25
Induction of labor or section	7	27	43	40	34	3
Induced before 38 weeks' gestation	6	20	28	16	8	1
Per cent induced before 38 weeks	30.0	30.0	32.8	18.4	9.2	3.8
Gestation 38 weeks or more†	11	16	38	61	75	24
Gestation less than 38 weeks	10	22	46	70	21	5
Per cent less than 38 weeks	47.6	55.0	54.8	31.5	22.7	17.3
No exchange transfusion	21	36	24	28	11	2
Exchange transfusion	0	4	61	62	91	28
Per cent exchange transfusion	..	10.0	71.8	68.9	89.2	93.4
Exchange transfusion repeated	0	0	0	0	11	6
Per cent repeated	..	..	..	..	12.1	21.4

* Unknown in 25 cases.
† Unknown in 8 cases.

been follow-up observation of at least four months in the case of each surviving baby.

RELATION OF EXCHANGE TRANSFUSION TO OCCURRENCE OF KERNICTERUS

In previous studies [18] we have indicated that during the first two years during which we used exchange transfusion in the treatment of erythroblastosis fetalis it was not possible to show with certainty that it had a favorable effect on mortality or on the frequency of kernicterus. On the other hand, it was shown that the avoidance of immaturity through failure to induce labor before term in the sensitized mother had probably been responsible for a lowering of mortality in liveborn infants, chiefly through the lowered incidence of kernicterus. The 15 month period (January 1949 to April 1950) which followed the period of the previous study (1945 to 1948) has seen the nearly complete disappearance of kernicterus from our series of babies treated by exchange trans-

fusion (table 1). Table 2 shows the strikingly lower incidence of kernicterus in infants treated with exchange transfusion. The value for chi-square is almost entirely the result of the differences in incidence of kernicterus.

TABLE 2.—*Relation of Exchange Transfusion to Outcome and to Other Factors of Importance in Erythroblastosis Fetalis*

	No Exchange Transfusion		Exchange Transfusion		Chi-Square	Degrees of Freedom*
	No.	%	No.	%		
Outcome						
Recovered, no sequelae	98	60.1	218	86.6		
Died, no kernicterus	2	2.5	11	4.5	8.37	2
Kernicterus, living or dead	21	17.2	17	6.9		
Gestation (unknown in 8 cases)						
Less than 36 weeks	13	11.0	18	7.4		
36 to 37 6/7 weeks	33	28	69	28.5	1.31	2
38 weeks and over	72	61.0	155	64.1		
Sex of baby						
Male	80	48.3	126	51.2	0.26	1
Female	68	51.7	120	48.8		
Maternal titer (unknown in 36 cases)						
Less than 1:16	45	40.0	42	18.0		
1:16 and 1:32	28	28.6	90	38.4	22.6	2
1:64 and higher	22	22.4	102	43.6		
Red blood cell count at birth (unknown in 22 cases)						
Less than 1,500,000/cu. mm.	0	....	26	10.6		
1,500,000 to 3,000,000/cu. mm.	11	12.0	90	36.9	34.3	2
Over 3,000,000/cu. mm.	81	88.0	128	52.5		
Hemoglobin (unknown in 73 cases)						
Less than 8 Gm./100 cc.	1	1.5	36	16.5		
8 to 12 Gm./100 cc.	14	18.2	85	39.0	28.8	2
Over 12 Gm./100 cc.	62	80.5	97	44.5		
Past history						
No erythroblastosis fetalis, no transfusions	77	69.1	116	47.1		
Sensitized by transfusion	12	9.9	34	13.8		
Erythroblastosis fetalis, recovered (1 or more)	23	18.9	60	24.4		
Erythroblastosis fetalis, died (1 or more)	8	6.6	28	11.4		
Kernicterus (1 or more)	4	3.3	19	7.7		
Stillbirth (1 or more)	4	3.3	21	8.5		
Severity of jaundice (unknown in 28 cases)						
None or slight	40	38.5	74	22.8		
Moderate	20	19.2	90	39.8	13.3	2
Marked	44	42.3	62	27.4		

* For 1 degree of freedom values for chi-square of 3.84 and 6.64 correspond respectively to the 5 per cent and 1 per cent levels of significance. For 2 degrees of freedom the values for chi-square denoting similar significance are 5.99 and 9.21.

It is practically certain that a decrease in the frequency of immaturity in the infants played a role in a lowered incidence of kernicterus (table 1). This factor and other factors of known significance with relation [1b,c] to the frequency of kernicterus are also dealt with in table 2. There is a slight excess of mature babies in the group treated by exchange transfusion, but this excess is not sufficient to account for the decreased frequency of kernicterus. It is not a significant excess, and, as shown in table 3, the decrease in the incidence of kernicterus has

occurred in both the immature and the more mature groups of infants. When the possible role of our present policy of not inducing labor is further evaluated by excluding from consideration infants of mothers with induced labors in both the group treated by exchange transfusion and the group not so treated, we have found that there was an actual deficit of mature babies in the group treated by exchange transfusion. There was still, however, a significant reduction of the incidence of kernicterus associated with exchange transfusion in these spontaneously delivered infants. And finally, the frequency of kernicterus was actually lower in the babies of mothers whose labors were induced, provided the babies were treated by exchange transfusion, than in the babies of mothers whose labors were not induced and whose babies were not treated by exchange transfusion.

TABLE 3.—*Relation of Exchange Transfusion to Gestation and Outcome*

	No Exchange Transfusion	Exchange Transfusion	Chi-Square	Degrees of Freedom
Gestation less than 36 weeks				
No kernicterus	7	14	....	..
Kernicterus	6	4	....	..
Per cent kernicterus	46	22	1.02	1
Gestation 36 to 37 6/7 weeks				
No kernicterus	22	61	....	..
Kernicterus	11	8	....	..
Per cent kernicterus	33	12	5.44	1
Gestation 38 weeks or more				
No kernicterus	68	150	....	..
Kernicterus	4	5	....	..
Per cent kernicterus	5.8	3.3	0.21	1
			6.67	3*

* For 3 degrees of freedom the values for chi-square of 7.814 and 11.341 correspond respectively to the 5 per cent and 1 per cent levels of significance.

There is seen to be a normal distribution of male and female infants.

The much higher maternal Rh antibody titers in the group treated by exchange transfusion results from definite selection of these babies for exchange transfusion, not only because the clinical disease was severer in such infants but also because a high maternal titer has itself been an indication for exchange transfusion. Therefore, the decrease in incidence of kernicterus in babies treated by exchange transfusion has occurred in spite of a factor predisposing to a high incidence of kernicterus. The fact that the red blood cell counts and hemoglobin levels were significantly lower in the group treated by exchange transfusion adds further weight to the evidence that this was, on the whole, a group of babies sicker than those not treated by exchange transfusion. The past histories of the group of infants treated by exchange transfusion would also seem to indicate that they had a worse prognosis than the other group.

The figures for the occurrence of jaundice, in table 2, show a decrease in the frequency with which "marked" jaundice was seen in babies treated by exchange transfusion. This was entirely due to a shift of babies from the group with "marked" jaundice to that considered "moderately" jaundiced. We feel that this difference would have been even more striking if our present practice of looking for jaundice under relatively controlled conditions (always by daylight, with a northern exposure, and with the baby entirely undressed) did not lead to the more frequent observation of severe jaundice in a group predominantly treated by exchange transfusion. The decrease in the severity of jaundice does not seem accidental, nor does it make sense unless it is the direct result of exchange transfusion. It will be shown below that this lessening of jaundice is the probable mechanism of prevention of kernicterus by exchange transfusion.

TABLE 4.—*Relation of Severity of Jaundice to Incidence of Kernicterus*

A. Degree of Jaundice*

	None or Slight	Moderate	Marked
No kernicterus	114	106	76
Kernicterus	0	4 (3.6%)	30 (28.3%)

(Chi-square equals 51.1 (2 degrees of freedom)

B. Breakdown of Cases with Marked Jaundice

	No Exchange Transfusion	Exchange Transfusion
No kernicterus	28	48
Kernicterus	16 (36.4%)	14 (22.6%)

* The degree was unknown in 28 cases, in 4 of which there was kernicterus.

RELATION OF JAUNDICE TO KERNICTERUS

Table 4 shows the relation of the severity of jaundice to the likelihood of kernicterus. The degree of jaundice recorded is the maximum seen during the first five days of life. Cases of stillborn babies and those dying during the first day of life and of those infants admitted to the Children's Hospital after the first 24 hours of age are omitted from consideration for the reasons given above, with the additional reasons that jaundice was never observed in stillborn infants, nor in liveborn infants at the moment of birth, and was rarely "marked" in babies dying before 24 hours of age. This relation of jaundice to kernicterus is the most striking of the clinical correlations we have seen. It has a consistent very close relation to each of the other clinical correlates of the occurrence of kernicterus, as is shown in tables 5, 6 and 8. Table 4 also indicates that kernicterus may be expected to occur in approximately 35 per cent of markedly jaundiced erythroblastotic babies when exchange transfusion is not given.

Table 5 reaffirms the increased likelihood of kernicterus when the maternal titer is high [1b] and shows that exchange transfusion has been associated with significantly lowered incidence of kernicterus when maternal titer was high ($\chi^2 = 5.6$). It is noteworthy that there is no longer seen a significant relation between titer and kernicterus in the

TABLE 5.—*Relation of High Maternal Titer to Increased Incidence of Kernicterus and to Increased Severity of Jaundice*

	Maternal Titer*					
	Less Than 1:64		1:64 or Higher		Chi-Square	Degrees of Freedom
	No.	%	No.	%		
Babies not treated by exchange transfusion						
No kernicterus	68	89.5	15	68.2	4.42	1
Kernicterus	8	10.5	7	31.8	....	..
Babies treated by exchange transfusion						
No kernicterus	125	94.7	92	90.2	1.13	1
Kernicterus	7	5.3	10	9.8	....	..
Jaundice†						
None or slight	77	41.0	29	30.2	....	..
Moderate	66	35.1	33	34.2	9.36	2
Marked	45	23.9	44	39.6	....	..

* The titer was unknown in 24 cases in which exchange transfusion was not used, and in 6 of these there was kernicterus. There was no kernicterus in 12 cases in which exchange transfusion was used and in which the titer was unknown. Of cases in which the titer was unknown, there was little or no jaundice in 8, moderate jaundice in 6 and marked jaundice in 17; in 5 the degree of jaundice was unknown.

† Among cases in which the maximum degree of jaundice was unknown, the titer was less than 1:64 in 20 and 1:64 or higher in 13.

TABLE 6.—*Relation of Immaturity to Increased Incidence of Kernicterus and to Increased Severity of Jaundice*

	Gestation*					
	38 Weeks or Over		Less Than 38 Weeks		Chi-Square	Degrees of Freedom
	No.	%	No.	%		
No kernicterus	217	95.6	105	79.0	20.9	1
Kernicterus	10	4.4	28	21.0		
Jaundice†						
None or slight	80	43.4	23	19.7	21.0	2
Moderate	66	33.2	41	35.0		
Marked	50	24.4	53	45.3		

* In 8 cases in which the gestation period was not known, none of the babies had kernicterus, 2 had little or no jaundice, 3 had moderate jaundice and 3 had marked jaundice.

† In 58 cases in which the maximum degree of jaundice was not known, 22 were mature, 16 had less than 38 weeks of gestation.

babies treated by exchange transfusion. This probably reflects again the value of exchange transfusion in the prevention of kernicterus. Finally, table 5 shows clearly that the higher maternal titers are associated with greater degrees of jaundice and suggests, with the data of table 4, that the increased jaundice associated with high titers may be the means by which the high titer exerts its malign effect.

Table 6 illustrates the important relation of immaturity to the likelihood of kernicterus in this group of infants. This is one of the few variables in erythroblastosis fetalis which is under the control of the physician, who must ordinarily refrain from induction of labor in the sensitized mother, especially before 39 or 40 weeks' calculated gestation. In this group of babies the incidence of kernicterus was barely one fifth as great in babies born after 38 weeks' gestation as in babies born before that time. Like the high maternal titer, the immaturity of the baby is associated with a very striking increase in the frequency with which severe jaundice is seen. Here, too, it is necessary to conclude that an increase in serum pigments may be the means by which immaturity leads to kernicterus in certain infants.

TABLE 7.—*Frequency of Erythroblastotic Stillbirths and of Fatal Erythroblastosis with Hydrops Fetalis at Boston Lying-in Hospital and Richardson House*

Year	Stillbirths	Hydrops (Died)	Percentage of Pregnancies Resulting in Stillbirth or Fatal Hydrops
1945	8	4	33
1946	12	1	30
1947	14	3	27
1948	14	2	25
1949	16	4	35

We had, of course, been worried that a policy of not inducing labor in the sensitized mother might lead to larger numbers of stillborn and hydropic infants, but we do not now find any reason to regret such a policy. Table 7 shows that there has been no significant change in the rate of stillbirths among sensitized women delivered at the Boston Lying-in Hospital or Richardson House during the last five-year period. This is in spite of the facts that there has been a constant increase in the number of mothers referred to these hospitals because of past difficulty with erythroblastosis fetalis and that the frequency of induction of labor in the sensitized mother has significantly decreased since the latter part of 1947.

Table 8 shows that the last major correlate of kernicterus, the sex of the baby, is like the maternal titer and immaturity in that there is a close association between an ominous character, maleness, and the degree of jaundice seen. Table 8 fails to illustrate the significant difference between male and female babies noted previously.[1c] Of our total group of 246 female babies, 8.9 per cent had kernicterus, as against 17.8 per cent of 269 male babies admitted before the age of 1 week.

TABLE 8.—*Relation of the Sex of Erythroblastotic Babies to the Outcome and to the Severity of Jaundice* *

	Female Babies		Male Babies		Chi-Square	Degrees of Freedom
	No.	%	No.	%		
Recovered, no sequelae....	164	89.6	133	85.2	3.15	2
Kernicterus, living or dead	14	7.7	24	15.0		
Died, no kernicterus.....	5	2.7	9	4.8		
Total livebirths.....	183		185			
Stillbirths†	25		37			
Jaundice						
Moderate or less.....	117	73.6	107	62.6	4.01	1
Marked	42	26.4	64	37.4		

* In the 38 cases in which degree of jaundice was not recorded, 24 babies were female and 14 were male.

† Boston Lying-in Hospital and Richardson House.

TABLE 9.—*Data on Cases Omitted from Statistical Analysis*

	Children's Hospital					Children's Hospital '47-'50, Boston Lying-in Hospital and Richardson House '45-'50
	1945 and 1946			1947 to 1950		
	Admitted Before 24 Hours	Admitted at 2 to 7 Days	Admitted After 7 Days	Admitted at 2 to 7 Days	Admitted After 7 Days	Died Before 24 Hours
No exchange transfusion						
Recovered, no sequelae....	10	21	20	30	25	..
Died before 24 hours*.....	4	..	..	..	..	20
Died after 24 hours*.....	1	3	0	2	1	..
Kernicterus	12	11	2	8	3	0
Exchange transfusion						
Recovered, no sequelae....	1	0	0	4	0	..
Died before 24 hours*.....	0	..	..	..	..	19
Died after 24 hours*.....	0	0	0	0	0	..
Kernicterus	0	0	0	1	0	0
Sex						
Male	16	25	10	23	18	20
Female	12	10	12	23	14	19
Gestation						
Less than 38 weeks.....	11	5	2	6	1	29
38 weeks or longer.....	17	28	18	35	28	9
Length unknown.....	0	2	2	4	3	1
Maternal titer						
Less than 1:16.....	4	6	1	8	4	4
1:16 or 1:32.....	6	6	0	13	6	12
1:64 or higher.....	5	5	2	3	6	15
Antepartum maternal titer unknown.....	13	18	19	21	16	8
Past history						
No previous erythroblastosis fetalis, not sensitized by transfusion.....	15	23	16	31	26	12
Sensitized by transfusion.	0	4	1	5	5	8
Erythroblastosis fetalis recovered (1 or more)..	7	4	4	5	2	12
Erythroblastosis fetalis, died (1 or more).....	5	2	0	2	0	7
Kernicterus (1 or more)...	1	1	0	0	0	1
Erythroblastosis fetalis, stillbirth (1 or more)...	1	1	1	2	1	9
Total cases.....	28	35	22	45	32	39

* No kernicterus.

RESULTS OF A PROGRAM FOR TREATMENT OF ERYTHROBLASTOSIS FETALIS

The data presented above show that severity of jaundice is a common denominator in all those situations in which the high frequency of kernicterus has been directly related to other variables and show that exchange transfusion, which lessens the severity of jaundice, is associated with less frequent kernicterus. It is necessary to consider whether a certain high level of serum pigment may not be essential for the development of kernicterus in a given infant. There is no reason, on the other hand, for believing that even an extremely high level of blood bilirubin will lead to kernicterus in a baby who is not in some way susceptible to injury by that substance. Some of the elements which might be associated with increased susceptibility to cerebral injury from bilirubin have been discussed in a previous report.[2] Whatever the fundamental disturbance in kernicterus may be, there remain to be explained (1) why kernicterus is not seen in stillborn babies or in babies dying before about 24 hours of age, many of whom have considerably elevated serum bilirubin levels, (2) why kernicterus does not occur in babies after about 5 days of life (rarely later), even in certain immature infants carrying a high level of serum bilirubin a month or more, and (3) why certain babies (perhaps 30 to 35 per cent of all babies) are not apparently susceptible to kernicterus in any circumstances.

If, as the data reported above seem to show beyond reasonable doubt, exchange transfusion lowers the incidence of kernicterus and if, as seems entirely likely, it exerts its beneficial effect through lessening hyperbilirubinemia, then a treatment program for erythroblastotic infants must use exchange transfusion in such a way as to make most effective its function of removing bilirubin from the baby's blood. It can no longer be doubted, as in the past, that Rh-negative blood must be used in the treatment of erythroblastosis fetalis due to the Rh factor. (Whatever the blood antigen system involved in a case of erythroblastosis fetalis, the blood used for treatment of the baby should be "negative" for that factor.) Group O blood has the advantages that it can be obtained before the birth of the baby and be held ready for immediate use and that it will not worsen the outlook for a group A or group B baby whose mother might be sensitized to A or B as well as to Rh. The soluble specific A and B polysaccharides [3] should be added to group O blood if it is to be used for a group A, group B or group AB baby. Fresh blood is desirable for exchange transfusions, since the survival time of transfused cells is maximum in fresh blood and since there may be free blood pigment in the plasma of old bank blood.[4] Recent studies of

3. We add 10 ml. of solution of A and B soluble specific substance (Sharpe & Dohme, Inc.) to each pint, (473 ml.) of group O blood.

4. We use bank blood up to seven days old but prefer fresh blood, especially for a second exchange transfusion (see below).

Allen, Diamond and Watrous [5] indicate that the blood of a female donor may be preferable to that of a male donor.[6]

The criteria for use of exchange transfusion can be rationally oriented to the problem of minimizing jaundice. An exchange transfusion should be started without delay when the Rh-positive baby of a sensitized Rh-negative mother shows pallor, hepatosplenomegaly, petechiae, edema or such anemia (less than about 4,500,000 red blood cells per cubic millimeter) as to make possible an unequivocal diagnosis of clinical erythroblastosis. If an Rh-positive baby has no clinical signs of illness, an exchange transfusion should be done if the maternal titer is high (1:16 or above in our laboratory), if the baby is immature (especially if less than 38 weeks' gestation) or if there is a past history of serious or fatal erythroblastosis fetalis in a previous infant. If other indications were equivocal, it would probably be wise to use exchange transfusion on a male baby when a female infant might be treated expectantly.

If exchange transfusion is not elected or done immediately after birth, it should be done at the earliest opportunity if jaundice appears during the first 24 hours of life. On an average obstetric service it is likely that any baby in whom jaundice develops during the first day of life or who has moderate or marked jaundice on the second day will be found to have erythroblastosis fetalis. It is important that nursing and medical personnel be alert to this fact so that prompt treatment can be given affected infants.

If after an initial exchange transfusion an infant with erythroblastosis fetalis shows increasing jaundice, it is likely that he may benefit from a second exchange transfusion. Our experience with second exchange transfusions at the time of writing of this report is limited to 25 cases, but the results fully justify a preliminary statement that jaundice in the mature [7] erythroblastotic infant can be brought under complete control by repeated exchange transfusions. We have generally performed the second transfusion about 12 to 18 hours after the first, both being done by the umbilical vein route. The second exchange transfusion, in

5. Allen, F. H., Jr.; Diamond, L. K., and Watrous, J. B., Jr.: Erythroblastosis Fetalis: V. The Value of Blood from Female Donors for Exchange Transfusion, New England J. Med. **241**:799-806, 1949.

6. We have used female donors exclusively since July 1949.

7. That jaundice may be difficult to control in the premature baby is illustrated by the case of a baby treated since these data were collected. The baby was delivered by section at 30 weeks' gestation for reasons other than the Rh sensitization. In spite of two exchange transfusions within the first 24 hours of life, jaundice became severe and definite clinical evidence of kernicterus developed. Three months' observation have made it almost certain that permanent brain damage exists, although clinical observation is made somewhat difficult because of retrolental fibroplasia.

addition to removing the principal source of new pigment (the baby's Rh-positive cells remaining after the first exchange plus those subsequently released from the marrow), removes about 25 per cent of the total bilirubin in the body. Jaundice has invariably faded with astonishing rapidity after two exchange transfusions done in the first 24 hours of life and has sometimes entirely disappeared within another 24 hours, even when marked before the beginning of the second transfusion.

Between April 1, 1949 and April 2, 1950, there were 109 Rh-positive babies of sensitized mothers treated by exchange transfusion in this clinic in the group presented in table 1, of whom 17 received multiple exchange transfusions (two transfusions in 15 cases, three in 2 cases). Of these 109 infants, kernicterus developed in only one (the mature, female infant of a mother with low titer [1:4], in whom severe jaundice developed after a single exchange transfusion done at 8 hours of age and who died of kernicterus on the fourth day).[8] It was this case which led us to the decision that increasingly marked jaundice after an initial exchange transfusion was a compelling indication for a second transfusion.

Of this group of 109 babies, 22 (20 per cent) were born after induced labor or cesarian section (sometimes for titer, sometimes for purely obstetric reasons) and only 8 (7.3 per cent) before 38 weeks. This is a smaller number than in previous years and undoubtedly plays some role in the favorable results. A total of 25 infants were born before 38 weeks' gestation. In 54 cases the maternal titer was 1:64 or higher; in 86 cases (79 per cent) the titer was 1:16 or higher. The generally higher titers reflect the use of the mother's high titer as a criterion for election of exchange transfusion.

Besides the single case of kernicterus, there were five deaths after 24 hours of age in this selected group of infants,[9] all of whom had very severe erythroblastosis fetalis, but no pathological or clinical evidence of kernicterus.

In addition to exchange transfusion, most of these infants received oxygen in high concentration and large doses of crude liver extract (1 ml. every eight hours for as long as five days). We have no reason to believe these measures necessarily helpful. It is not possible to say whether the use of female donor blood had played any determinant role in the good results seen in this group of cases.

8. A second exchange transfusion, done 18 hours after the appearance of clinical signs of kernicterus, failed to alter the course. There is no evidence that the severe jaundice in this baby was the result of the first exchange transfusion. The blood, from a regular and repeatedly tested donor, had been drawn on the day of the transfusion.

9. Seven babies, whose cases are omitted from table 1, died before 24 hours of age. All were severely ill; six were moribund before the transfusion was started, and four had marked hydrops.

It is clear that in evaluating the results of any program of therapy such as that outlined above there are imponderable variables which make it difficult to use statistical methods with unbridled optimism. The results we have seen, however, give us every reason to feel that kernicterus will not prove to be a serious problem in the future, since it is virtually confined to those infants who have marked jaundice in the neonatal period and since in erythroblastotic infants prompt and otherwise appropriate use of exchange transfusion, repeated as indicated, will modify icterus in intensity and duration in such a way as to avert kernicterus.

SUMMARY

Data are presented which show that there has been a decrease in the incidence of kernicterus in erythroblastosis fetalis with the use of exchange transfusion.

It is shown that severe jaundice is a common denominator in those situations in which the frequency of kernicterus has been related to other variables.

Exchange transfusion probably exerts its beneficial effect so far as kernicterus is concerned through minimizing the tendency for erythroblastotic infants to become markedly jaundiced.

In the light of these observations a rational program for the management of erythroblastosis fetalis is outlined. It includes the rigid avoidance of early induction of labor, the use of exchange transfusion with Rh-negative blood from female donors for any babies felt likely to have severe icterus and the use of second exchange transfusions when increasingly marked jaundice is seen following an initial exchange transfusion.

The preliminary results of such a program are presented, which record only one case of kernicterus in a group of 109 liveborn infants with erythroblastosis fetalis. It seems entirely probable that kernicterus can be practically eliminated as a complication of erythroblastosis fetalis.

Case Reports

CONGENITAL PULMONARY STENOSIS WITH INTACT INTERVENTRICULAR SEPTUM

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AND
W. T. McCOLLUM, M.D.
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Stenosis of the pulmonary valve as the sole or major anomaly has been recognized for many years as one of the more uncommon forms of congenital heart disease. It occurs much more frequently in association with an interventricular septal defect, usually as a component of the tetralogy of Fallot. According to the recently published bibliography [1] and Maude Abbott's pioneering study of congenital heart disease,[2] the first case of pulmonary stenosis with patent foramen ovale and intact interventricular septum was published about one hundred years ago by Peacock.[3]

In her analysis of 1,000 cases of congenital heart disease, Abbott found 16 such cases, with an additional 9 cases of pulmonary stenosis in which both the septums were closed. This total of 25 cases in which the intervetricular septum was closed was in sharp contrast to the 85 cases of pulmonary stenosis associated with defects of the interventricular septum; 51 cases had closed foramen ovale and 34 cases had patent foramen ovale. That these facts are not widely recognized, and hence may lead to erroneous clinical diagnoses, was recently pointed out by Currens, Kinney and White.[4] Auerbach and Harper [5] in reporting a case similar to the one described here also pointed out this relative incidence in Abbott's series and emphasized the clinical diagnostic difficulties. The usual error seems to lie in the assumption that cases showing pulmonary stenosis and right ventricular hypertrophy are examples of the commoner tetralogy of Fallot, with little consideration of the possibility of an uncomplicated pulmonary stenosis.

From the Departments of Pathology and Medicine, University of Oklahoma School of Medicine.

1. Bauer, D. de F., and Astbury, E. C.: Congenital Cardiac Disease: Bibliography of One Thousand Cases Analyzed in Maude Abbott's "Atlas," with Index, Am. Heart J. **27**:688-732, 1944.

2. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

3. Peacock, T. B.: Contraction of the Orifice of the Pulmonary Artery, and Communication Between the Cavities of the Auricles by the Foramen Ovale, Tr. Path. Soc. London **1**:200-203, 1848; cited by Bauer and Astbury.[1]

4. Currens, J. H.; Kinney, T. D., and White, P. D.: Pulmonary Stenosis with Intact Interventricular Septum: Report of Eleven Cases, Am. Heart J. **30**:491-510, 1945.

5. Auerbach, S. H., and Harper, H. T.: Congenital Pulmonary Stenosis with Closed Interventricular Septum: Report of a Case Associated with Patent Foramen Ovale and Slight Tricuspid Stenosis, Am. Heart J. **34**:131-137, 1947.

It is felt that the report of another case of congenital pulmonary stenosis in a 7 month old infant in which the clinical diagnosis was in error is justifiable.

REPORT OF A CASE

H. L. F., a 7 month old white male infant, was admitted to the University Hospital on Dec. 17, 1946. The mother stated that he had been a "blue baby"

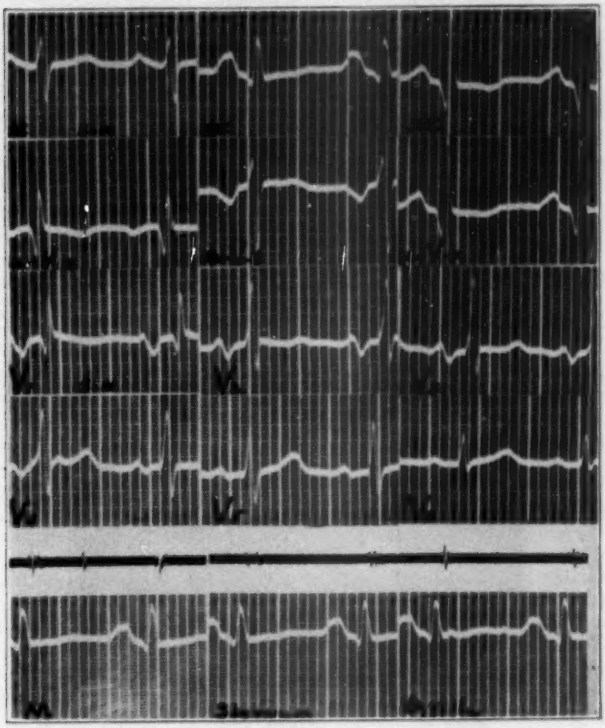

Fig. 1.—Electrocardiogram and sound tracing showing right ventricular hypertrophy and systolic murmur.

since birth and that he had had a cough ever since he was born and episodes when "he could not get his breath." He "coughed up blood" for the first time on the date of his admission and for this reason was brought to the hospital. The family history was noncontributory, except for the fact that the maternal uncle was a "blue baby"; the mother, father and three siblings were living and well. Specifically, the pregnancy was not complicated by measles, smallpox or other infectious disease. At birth, the child was a full term infant, weighing 9 pounds (4,082 Gm.).

Physical examination revealed a well developed, seriously cyanotic infant. The veins of the optic fundi were greatly distended. Moist rales were audible in the bases of both lungs. The heart was moderately enlarged with a rate of 182. A harsh systolic murmur was heard best at the apex and was distinctly audible at the aortic area. The liver was palpable 2½ fingerbreadths below the costal margin. There was slight pulmonary osteoarthropathy.

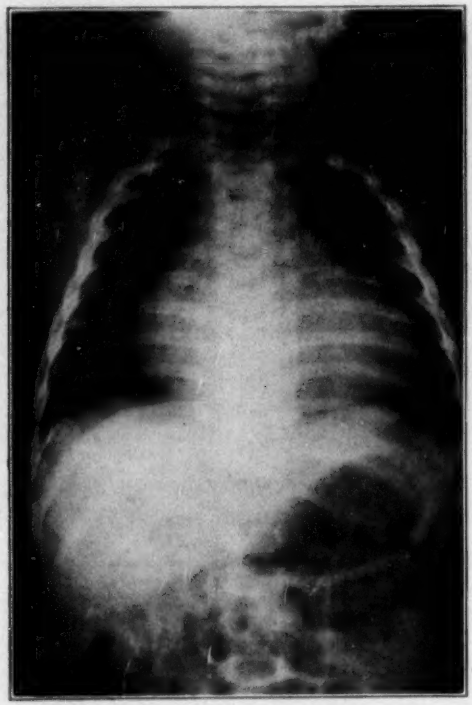

Fig. 2.—Roentgenogram of chest showing generalized enlargement of cardiac silhouette.

Significant laboratory data on December 18 revealed a 3 plus reaction for albumin in the urine. The red blood cell count was 6,930,000, with 15.5 Gm. of hemoglobin. The white blood cell count was 7,000, with a normal differential count. An electrocardiogram (fig. 1), utilizing Wilson's terminal and exploring the six standard precordial positions, showed striking right ventricular hypertrophy. The prominent Q and tall R waves at V_1 and the broad S wave present from V_1 through V_6 were the basis for such a diagnosis. The transition zone from the right precordium (right ventricle) and the left precordium (left ventricle) was between V_2 and

V_6. The heart was in the horizontal position. There was a right axis deviation in the limb leads, with a prominent P wave in the limb and the precordial leads, indicative of auricular hypertrophy. The sound tracing (lower part, fig. 1) showed a harsh, high-pitched, systolic murmur at the mitral area, distinctly audible over the sternum, 6 cm. medial to the apex, and barely perceptible in the axilla, 6 cm. lateral to the apex. It was suggestive but not diagnostic of the murmur of interventricular septal defect.[6] A roentgenogram of the chest (fig. 2) showed generalized enlargement of the cardiac silhouette, moderate to extreme with a globular configuration. Dr. R. H. Bayley stated, "The combination of marked right ventricular hypertrophy, murmur of septal defect and cyanosis 'strongly suggest' tetralogy of Fallot."

Digitalization was started the day of the infant's admission in view of the decompensation, and the response seemed to be good for a few days. However, gradually increasing cyanosis, dyspnea and suppression of breath sounds in the right lung supervened and the child died on the ninth day in the hospital. The final clinical diagnosis was congenital heart disease: tetralogy of Fallot with cardiac failure.

Autopsy.—The final anatomic diagnosis was as follows: (1) congenital cardiac anomaly characterized by (*a*) pronounced pulmonary stenosis, (*b*) extreme hypertrophy of the right ventricle and atrium, (*c*) scarring and moderate stenosis of bicuspid right atrioventricular valve and (*d*) anatomically and physiologically patent foramen ovale, and (2) chronic passive congestion of viscera.

The pertinent findings were confined to the heart, which weighed 80 Gm. (estimated normal weight, 34 Gm.). Approximately five sixths of the anterior surface consisted of the enormously dilated and hypertrophied right atrium and ventricle which made up the right border and apex (fig. 3). The right atrium, the largest of the cardiac chambers, measured 4 cm. in all diameters. Its wall was 0.3 to 0.4 cm. thick (fig. 4). The tricuspid valve measured 5 cm. in circumference. There was an apparent fusion of the septal and posterior cusps, forming two fairly well defined cusps. These were considerably thickened and fibrosed, especially toward their free borders, as were their chordae tendineae which were thickened and shortened (fig. 4). The wall of the right ventricle measured 1.2 cm. in thickness. The three cusps of the pulmonary valve were fused along their contiguous surfaces, forming a cone-shaped diaphragm with an elliptic orifice at the apex, measuring 0.2 by 0.1 cm. (fig. 5). Otherwise, the cusps did not appear grossly thickened or scarred but were relatively thin and pliable. The circumference was 1.8 cm. The pulmonary artery and its branches were normal in size and distribution. The ductus arteriosus was closed. The foramen ovale was anatomically and physiologically patent but was partially closed by a thick fibrous valvelike fold on its left atrial aspect.

No anomalies were observed in the left side of the heart, aorta or coronary vessels. The mitral valve was normally formed, measuring 5.5 cm. in circumference. The wall of the left ventricle was 0.8 cm. in thickness. The interventricular septum was intact (fig. 4). The normal aortic valve measured 2.7 cm. in circumference. Vegetations were not present on any of the valve cusps.

Microscopic examination showed normal architectural arrangement of the muscle, considerable interstitial edema and slight diffuse interstitial hemorrhage. The venous sinusoids were prominent. The muscle fibers themselves were rela-

6. Sound tracings were not recorded over the aortic or pulmonary areas since "stethetron" study suggested the recordings made.

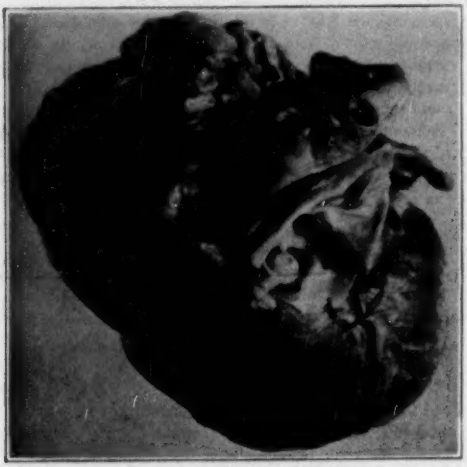

Fig. 3.—Anterior view of heart illustrating relative size of right atrium and ventricle. The pulmonary artery has been opened to demonstrate the pulmonary valve.

Fig. 4.—View of opened right atrium and ventricle. Note dilatation and hypertrophy of both chambers and thickening of cusps of "bicuspid" atrioventricular valve.

tively large and showed focal areas of degeneration characterized by a pale-staining granular cytoplasm, with a loss of distinctness of striations. There was a slight to moderate diffuse interstitial fibrosis throughout the myocardium. The leaflets of the tricuspid valve were irregularly thickened and distorted by a dense collagenous connective tissue in which nuclei were sparse. This process extended to a slight degree into the myocardium about the valve ring. There was no evidence of any active inflammatory reaction in any area, nor were there any changes suggesting a specific etiologic agent for the scarring.

Fig. 5.—Opened pulmonary artery showing stenotic pulmonary valve. Note fusion of contiguous surfaces of cusps with small orifice at apex.

COMMENT

The configuration of the stenotic pulmonary valve in this case is one of the most interesting features, especially in view of the discussion in the present day literature on the etiologic basis and pathogenesis of such cardiac malformations. As Currens and his associates [4] pointed out, it seems that congenital stenosis of the pulmonary valve falls into two general types. In one, the commoner, the pulmonary valve ring is narrowed, with scarring and distortion of the leaflets and ring, as in 9 of their 11 cases. In the second, and more unusual type, the malformation seems to consist essentially of a fusion of the contiguous surfaces

of the valve cusps without notable scarring or distortion, forming a cone-shaped diaphragm with a small orifice at the apex. This is the type of change seen in the case herein reported. It was described and pictured by Abbott [2] and observed by Currens and his associates [4] in 2 of their 11 cases and in cases recently reported by Freed and Budnitz,[7] Rossman,[8] Garrison and Feldt,[9] Blackford and Parker [10] and Auerbach and Harper.[5]

The occurrence of these two different types of pulmonary stenosis might be interpreted as the consequences of two different etiologic processes. The first type, with gross scarring and distortion, might be more in keeping with the idea of healed fetal endocarditis, while the second type, with fusion of well formed cusps, resembles more that which might be expected if the change were on the basis of a developmental defect. An attempt to make such a distinction, however, seems unjustifiable, particularly in view of the not uncommon involvement of the tricuspid valve, which in this case did show gross scarring and deformity with moderate stenosis. It seems most likely that all these changes are the consequences of the same underlying etiologic factor. In discussing conditions of this type, Abbott [2] stated that they were practically always inflammatory, a sequela of fetal endocarditis; she pointed to the frequent similar involvement of the tricuspid valve. There seems to be general agreement, however, among recent authors (Gross [11]; Currens and his associates [4]; Rossman [8]) that the concept of fetal endocarditis as the etiologic agent in the genesis of congenital cardiac malformations must be abandoned. No evidence of any active or specific inflammatory process was seen in the microscopic examination in this case. The maternal history was quite definite in stating that the pregnancy was uncomplicated by measles, smallpox or other infectious disease. However, one must always keep in mind the mildness of the streptococcic infections of the nasopharynx which may be seen as an etiologic basis for acute episodes and exacerbations of rheumatic carditis. It is well known that these mild infections are sufficient to produce such consequences in rheumatic disease.

From a clinical standpoint, this combination of congenital cardiac anomalies does not lend itself well to differential diagnosis. Differentiation of this condition from tetralogy of Fallot seems unlikely, since in both instances one is dealing with severe cyanosis from birth, right ventricular hypertrophy and a harsh systolic lower precordial murmur and sees a globular cardiac silhouette, a normal-sized aorta and absence or relative absence of the pulmonary conus on roentgenogram. In both instances there is a right to left shunt.

The actual location of the murmur would seem to be diagnostic from a theoretic standpoint but, practically speaking, this is not always true. Again, the trans-

7. Freed, A. N., and Budnitz, J.: Pure Congenital Pulmonary Stenosis: Case Report, Am. Heart J. **31**:369-372, 1946.

8. Rossman, J. I.: Congenital Atresia and Stenosis of Great Cardiac Vessels: Aortic Atresia; Pulmonary Stenosis, Am. J. Dis. Child. **64**:872-880 (Nov.) 1942.

9. Garrison, R. E., and Feldt, R. H.: Congenital Pulmonary Stenosis with Closed Cardiac Septa: Report of a Case with Comments Regarding the Circulation Time, Am. Heart J. **24**:685-688, 1942.

10. Blackford, L. M., and Parker, F. P.: Pulmonary Stenosis with Bundle Branch Block: Report of a Case with Sound Tracings and Semiserial Studies of Conduction Bundle, Arch. Int. Med. **67**:1107-1118 (June) 1941.

11. Gross, P.: Concept of Fetal Endocarditis: General Review with Report of Illustrative Case, Arch. Path. **31**:163-177 (Feb.) 1941.

mission of the murmur should give valuable aid, but in congenital heart disease this frequently fails.

Fluoroscopy in this case might have shown the extremely prominent right atrium. The electrocardiogram did reveal evidence of atrial hypertrophy. Possibly more weight should have been given this point. Hypertrophy of the right atrium occurred in 69 per cent of Abbott's [2] collected cases of the type under consideration here and in only 39 per cent of the cases of tetralogy of Fallot. When both the foramen ovale and the interventricular septum remained patent, the right atrium was found to be hypertrophied in 35 per cent of the cases. In single cases these percentages are of little value, but they do emphasize the importance of fluoroscopy when the patient's condition permits. When atrial hypertrophy is present on the electrocardiogram, fluoroscopy should be considered more seriously if it is not done routinely.

In this case it seems unlikely that a correct clinical anatomic diagnosis could have been made from the data available.

SUMMARY

A case of congenital pulmonary stenosis with patent foramen ovale and closed interventricular septum in which the clinical diagnosis was in error is presented. The incidence of this anomaly is discussed. Conflicting views concerning etiology are mentioned. Difficulties in clinical differential diagnosis are outlined and suggestions which might lead to more correct diagnoses are offered.

16 The Downs, Wimbledon, S. W. 20, London, England (Dr. Brown).

CONGENITAL LYMPHATIC LEUKEMIA

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Leukemia occurring in infancy is quite uncommon. The clinical manifestations are the same as those in the adult, except for the acute fulminating course which the disease always runs. Cross [1] in 1944 was able to collect 23 cases of congenital leukemia from a survey of the literature. Only 3 of these were of the lymphatic variety. Kelsey and Andersen [2] in 1939 reviewed the literature on leukemia occurring in the neonatal period. They were of the opinion that the following criteria should be present before one can call an early developing leukemia a "congenital leukemia." Clinically, the symptoms should present themselves either at birth or within a few days after birth. There should be hepatomegaly, splenomegaly and enlarged lymph nodes. The peripheral blood should show leukocytosis with the presence of immature cells. The history should be free of any indication of syphilis, icterus gravis neonatorum or erythroblastosis. Histologically, there should be more cellular infiltration than could plausibly have occurred in the extrauterine life. There should be an increase in the number of immature cells rather than a mere increase in the hemopoietic centers. Cellular infiltration should involve nonhemopoietic organs, as well as the liver, spleen and lymph nodes.

I have recently had the opportunity to study a case of leukemia of the neonatal period which conforms to these criteria. The clinical picture was that of an acute lymphatic leukemia. This was verified by the observations at autopsy.

REPORT OF A CASE

K. E., a white female infant, was born at Milwaukee Hospital on July 22, 1948. On August 30 she was admitted to the pediatric ward (service of Dr. R. M. Hall) where she died on September 2, at the age of only 42 days.

The parents were in good health with no family history of bleeding or of neoplastic disease. The infant was the result of the first pregnancy. The gestation period was of normal duration. Labor lasted thirteen hours eighteen minutes and was uneventful. Low forceps delivery was effected. The child appeared to be a normal full term girl in good condition. Her cry was spontaneous and lusty. Physical examination at this time revealed no anomalies. The liver and spleen were not palpable. The weight at birth was 8 pounds 6½ ounces (3,813 Gm.). No blood studies were made. The baby's stay in the nursery was unremarkable except for a small amount of vaginal bleeding which was noted on July 27. She was discharged with the mother from the hospital on that day. Her weight at that time was 8 pounds 1½ ounces (3,721 Gm.).

About two weeks after discharge the mother noted some "bumps" or "small bruises" developing on the surface of the child's body. These disappeared in a

From the laboratory of the Milwaukee Hospital.

1. Cross, F. S.: Congenital Leukemia, J. Pediat. **24**:191, 1944.

2. Kelsey, W. M., Jr., and Andersen, D. H.: Congenital Leukemia, Am. J. Dis. Child. **58**:1268 (Dec.) 1939.

few days and the mother was not alarmed. Up to that time the infant had been lively; she had taken her feedings well and steadily gained weight. During the following week, however, the child became increasingly irritable, cried more than usual, ate poorly and did not sleep well. Once again "bluish spots" appeared over the surface of the body. On August 23 a physician was called.

Physical examination revealed only one small area of purpuric discoloration on the chest and a rectal temperature of 102 F. Three days later, however, he noted many small purpuric areas scattered over the thorax. The liver and spleen could now be easily felt. The circumference of the abdomen increased appreciably. The child's condition failed to improve, and the temperature remained elevated. Therefore, on August 30 the infant was admitted to the pediatric service for diagnosis and treatment, with the provisional diagnosis of thrombopenic purpura.

Physical examination on her admission revealed an acutely ill, restless female child weighing 11 pounds (4,990 Gm.). There was moderate dehydration. The temperature was 103 F. rectally; the pulse rate was 170 and regular. There were numerous purpuric spots scattered diffusely over the body, most prominent over the anterior part of the thorax. The conjunctivas and mucous membranes were free of hemorrhage. The lungs were clear. The abdomen was distended, and the liver and spleen were quite large and easily palpated.

The laboratory findings are summarized as follows:

	Aug. 30, 1948	Sept. 1, 1948
Hemoglobin, Gm./100 cc.	8	6
Red blood cell count	2,700,000	2,040,000
White blood cell count	23,500	7,200
Lymphocytes, mature, %	94.5	94.0
Lymphocytes, young, %	3.0	0.5
Lymphoblasts, %	1.0	3.5
Monocytes, %	0.5	0
Segmented polymorphonuclear leukocytes, %	0	0.5
Metamyelocytes, %	0	0.5
Normoblasts, %	0	0
Thrombocytes	150,000	
Bleeding time	2 min. 30 sec.	
Coagulation time	3 min. 30 sec.	

Her blood was group O, Rh positive. All serologic reactions were negative. The heterophil antibody test also gave negative results. Urinalysis showed no abnormality except for a few red blood cells in the sediment.

Large doses of penicillin were given and continuous administration of oxygen was started. Fifty cubic centimeters of fresh whole blood was administered intravenously. Despite these measures, the clinical appearance of the infant became progressively worse. The temperature remained elevated. The infant was exceedingly restless, cried feebly and coughed frequently. Aspiration had to be done at frequent intervals. On the last day of life, the temperature dropped suddenly and the respirations became shallow and rapid. Death occurred on the morning of September 2.

Autopsy Observations.—The autopsy was performed three hours after death. Gross Examination: There were many purpuric hemorrhages scattered over the entire body, particularly on the trunk. There was no icterus. The abdomen was moderately distended. On opening the body, a small amount of fluid was seen in the body cavities. The lungs were dark red and hemorrhagic in appearance

and showed little or no crepitation. There was a small amount of fibrinous exudate on the pleural surface of the right lung. The liver weighed 500 Gm. It extended down below the costal margin for a distance of 5 cm. The organ was essentially normal in appearance except for this large size. The spleen weighed 150 Gm. There were some adhesions to the lateral abdominal well. The organ was firmer than normal, and on section the cut surface was a uniform dark red. The malpighian follicles were not seen. The kidneys were slightly enlarged and pale. Their combined weights were 110 Gm. On section the normal architecture could be seen. The bone marrow was gray. Both ovaries were enlarged and composed entirely of thin-walled follicular cysts. The lymph nodes were enlarged, particularly in the peritracheal and hilar regions. The largest nodes measured 5 mm. in diameter. The remaining organs showed no gross lesion.

Microscopic Examination: The microscopic examination revealed an extensive diffuse cellular infiltration which involved the subepithelial tissues of the skin in the areas where hemorrhage had been visible grossly, the liver, spleen and kidneys. Less extensive infiltrations were seen in the medullary portions of the adrenal glands, pancreas and uterine myometrium. These cells appeared to be small lymphocytes. Included among the cells, however, were a few larger ones which had the histologic appearance of lymphoblasts. The lymph nodes showed considerable distention of the blood vessels and lymph channels. The normal architecture of the nodes had been obliterated. No germinal follicles were seen; instead a diffuse overgrowth of small lymphocytes was noted. Sections of the bone marrow showed that the normal cells of the marrow were completely replaced by lymphocytic cells. No granulocytes were observed, but a few small areas of erythropoiesis and a few large megakaryocytes were still visible. The lungs showed no leukemic infiltration except for a few small peribronchial areas. The major change in the lungs was a diffuse hemorrhage involving almost all the alveoli. In one or two of the sections colonies of staphylococci were visible, growing in the center of the hemorrhagic areas. There was no leukocytic reaction around the colonies. No lymphocytes were visible in these areas.

SUMMARY

A case of congenital lymphatic leukemia is reported. There was no evidence of blood dyscrasia at birth. Symptoms appeared at the age of approximately 21 days, with the development of purpuric spots. No inflammatory processes were observed on examination of the child. The clinical picture was that of a lymphocytic leukemia. This was confirmed by observations at autopsy. Death occurred on the forty-second day of life.

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MECONIUM ILEUS

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Meconium ileus, first described by Landsteiner in 1905, refers to the neonatal form of fibrocystic disease of the pancreas and presents the clinical picture of intestinal obstruction due to inspissation of meconium in the small bowel and, to a lesser degree, in the proximal portion of the colon. The condition is relatively rare, the disorder in the present patient being the only one so diagnosed at Duke Hospital among 450,520 patients and more than 5,600 autopsies.

A review of the literature has not been undertaken since this was done recently by Wiglesworth,[1] whose excellent paper should be consulted by anyone interested in fibrocystic disease of the pancreas in general or meconium ileus in particular. The most significant contribution since the aforementioned review has been that of Baggenstoss, Power and Grindlay,[2] whose work will be considered in the comment following the case report.

REPORT OF A CASE

A 2 day old white female child, delivered at home, was admitted to the pediatric service of Duke Hospital, with a history of persistent vomiting, abdominal distention and absence of bowel movements since birth. Physical examination revealed the pulse rate to be 110, the temperature 37 C. (98.6 F.) and the respiratory rate 30. The infant was well developed and somewhat dehydrated, but in no apparent distress. The abdomen was distended, most notably in the epigastrium, and was hyperresonant. No masses or organs were palpable, and abdominal tenderness was absent. The results of the remainder of the physical examination were noncontributory. Accessory clinical findings were 17.6 Gm. of hemoglobin per hundred cubic centimeters and 4,950,000 erythrocytes and 3,600 leukocytes per cubic millimeter. Urinalysis showed nothing abnormal. The carbon dioxide-combining power was 57 volumes per cent; total proteins measured 5.9 Gm. per hundred cubic centimeters. Roentgenologic studies showed numerous dilated loops of small intestine, but nothing else of note.

Supportive measures, including parenteral administration of fluids, were instituted. On the second day in the hospital an exploratory laparotomy was performed, and the distal half of the ileum was observed to be filled with inspissated meconium. After evacuation of this material, the abdomen was closed, and the child, apparently in good condition, was returned to the ward. One hour after the operation the patient became cyanotic and her respirations labored. Resuscitative measures were of no avail, and the child died fifteen minutes later.

From the Department of Pathology, Duke University School of Medicine.

1. Wiglesworth, F. W.: Fibrocystic Disease of the Pancreas, Am. J. M. Sc. **212**:351-365 (Sept.) 1946.

2. Baggenstoss, A. H.; Power, M. H., and Grindlay, J. H.: The Relationship of Fibrocystic Disease of the Pancreas to a Deficiency of Secretin, Pediatrics **2**:435-442 (Oct.) 1948.

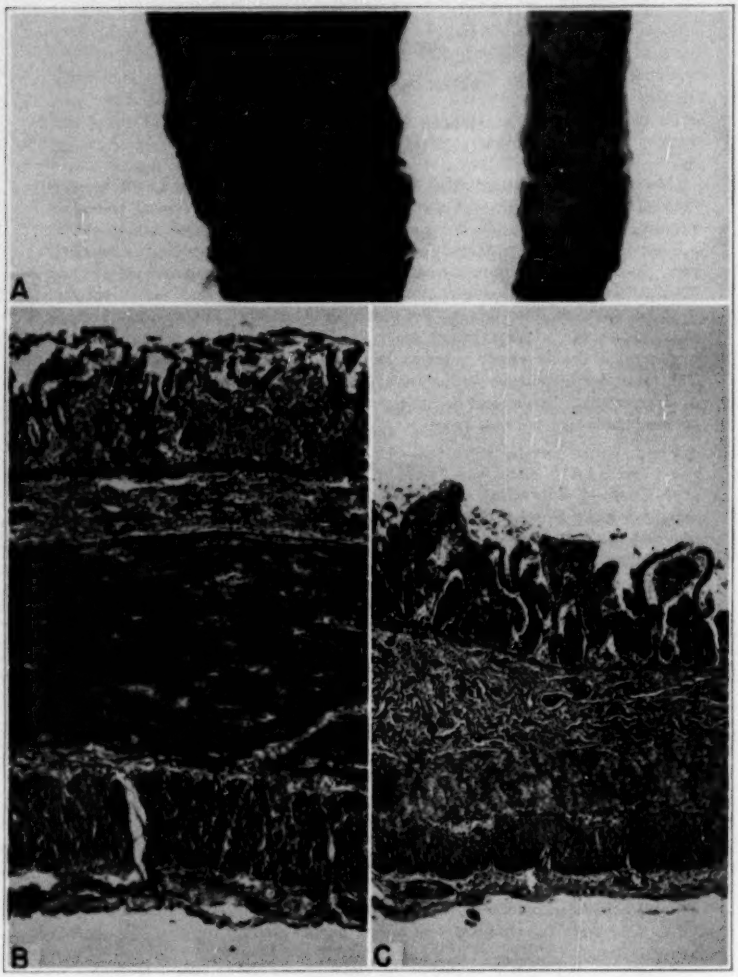

Fig. 1.—Sections of small intestine. *A*, photograph of jejunum (right) and ileum (left). The ileum is greatly dilated and the mucosal folds are prominent. In contrast, the proximal portion of the small intestine is normal. *B*, photomicrograph of terminal part of ileum to show mucosal and submucosal congestion and great hypertrophy of the muscularis; × 75. *C*, photomicrograph of jejunum which, in contrast to *B*, presents a normal appearance: × 75.

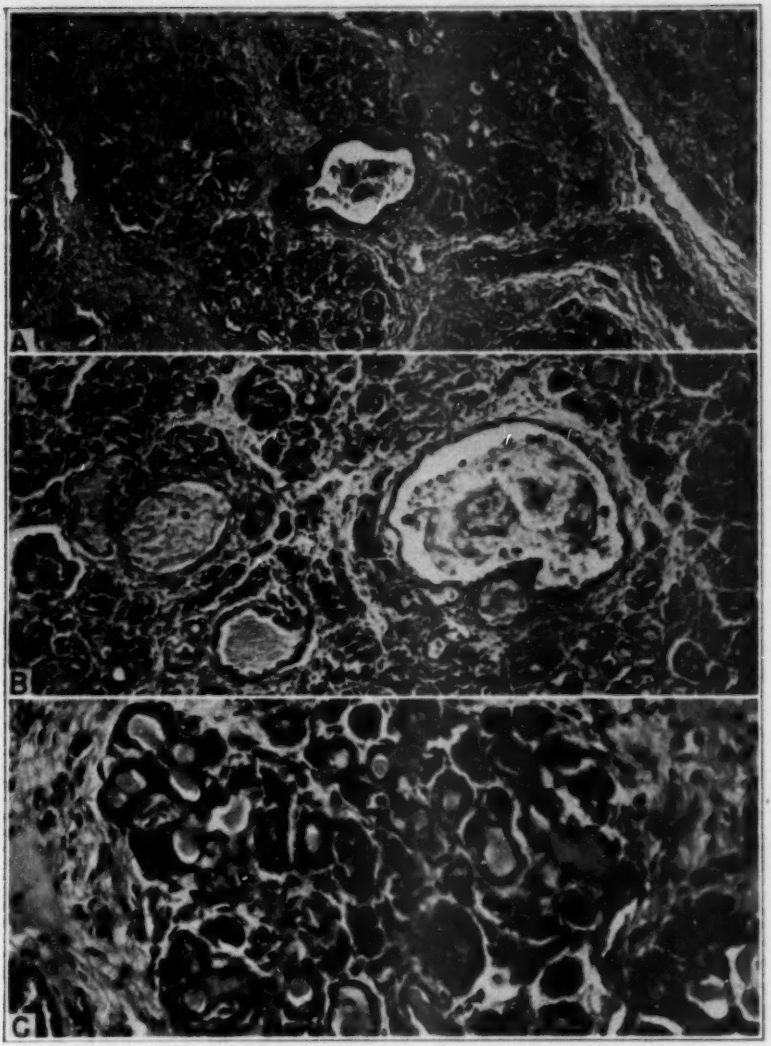

Fig. 2.—Sections of pancreas. *A*, low power view showing great deviation from the normal pattern. Note the prominent fibrosis, cystic dilatation of the ducts and acini and inspissated homogeneous material in these spaces; × 75. *B*, dilated ducts lined by flattened epithelial cells and containing inspissated secretion; × 142. *C*, similar inspissated material in the acini. Note the increased interlobular and intralobular connective tissue, in which are seen a few chronic inflammatory cells; × 335.

Autopsy (infant with history of intestinal obstruction since birth; exploratory laparotomy; cystic fibrosis of pancreas; meconium ileus, and dilatation, hypertrophy, congestion and edema of ileum).—Gross Examination: Autopsy was performed fifteen and a half hours after death by one of us (H. B.). The body was that of a 3 day old white female infant, weighing 3,100 Gm. and measuring 60 cm. in length from crown to heel. A right rectus incision, closed with black surgical silk, was noted. The abdominal cavity contained 100 cc. of serosanguineous fluid, and the serosal surface of the ileum was mottled dusky red. The stomach and duodenum contained green mucoid material. The jejunum was not remarkable. The ileum was extremely hypertrophied, but the mucosal pattern was not unusual. The lumen was greatly dilated and contained a few strands of inspissated, putty-like pale green meconium (fig. 1 *A*). The colon was in its normal location and was contracted throughout its course. The pancreas was not enlarged, nor were any cysts seen grossly. The pancreatic ducts appeared patent. The remainder of the gross autopsy observations were normal.

Microscopic Examination: Sections were stained with hematoxylin and eosin, Masson's trichrome stain, Foot's reticulum stain and Mallory-Wright glycogen stain. The ileum showed much edema and congestion of its wall, most prominent in the submucosa. The most striking change was a pronounced hypertrophy of the muscle layers, both longitudinal and circular (fig. 1 *B*). In contrast, the jejunum, save for minimal edema and stasis, was normal (fig. 1 *C*). Sections of the pancreas revealed a great deviation from the normal histologic pattern (fig. 2 *A*). Many of the ducts and acini were dilated and contained granular eosinophilic concretions (fig. 2 *B*), with resultant compression of the lining cells (fig. 2 *C*). There was extreme periductal, interlobular and intralobular fibrosis, the connective tissue containing small numbers of lymphocytes but no acute inflammatory cells (fig. 2). No other microscopic abnormalities were detected.

COMMENT

The history and findings in this case were typical. The presenting clinical picture was one of intestinal obstruction, with nausea and vomiting, distention and absence of flatus and meconium. At autopsy the ileum contained meconium having a "putty-like" consistency. The lumen was dilated, and the muscularis showed a pronounced degree of hypertrophy. In contrast, the colon was contracted and empty. Changes in the lungs (bronchiectasis, bronchopneumonia, abscess formation) and liver (fatty metamorphosis, biliary cirrhosis, proliferation of bile ducts), common in patients of the older age groups with fibrocystic disease of the pancreas, were not seen, due, no doubt, to the early age at which this child died.

The pathognomonic lesions seen in the pancreas consisted of an accumulation of eosinophilic secretion in the acini and ducts, pressure atrophy of the acinar tissue and fibrosis, due either to an absolute increase in connective tissue or to a relative increase secondary to the atrophy and disappearance of acinar elements. The lack of external pancreatic secretion resulted in failure of liquefaction of the meconium, its accumulation and impaction in the intestine and, finally, intestinal obstruction.

Numerous theories have been advanced to explain the absence of pancreatic juice from the intestinal lumen in these cases. These include (1) infection, (2) vitamin A deficiency, (3) congenital atresia of the pancreatic ducts, (4) abnormal pancreatic secretion and (5) congenital deficiency of secretin. The first four of these are fully discussed in Wiglesworth's paper.[1] The theory of an abnormal pancreatic secretion appeared best to explain the observed data. According to this hypothesis, overactivity of the vagus, due either to a disturbance of parasympa-

thetic innervation or to an autonomic imbalance in nervous control of pancreatic secretion, leads to the production of a thick viscid juice which subsequently becomes inspissated and blocks the acini and ducts.

In 1948, Baggenstoss and his co-workers [2] suggested that the absence of pancreatic juice was the result of an intrinsic obstruction secondary to a congenital deficiency of secretin. It is well known that the exocrine pancreatic secretion is stimulated by the vagal fibers and by secretin, and that these excitor agents occasion the flow of pancreatic juices differing in physical and chemical properties. "Vagal juice" is thick and viscid, while "secretin juice" is watery and has both a diluting and a flushing effect. If secretin is lacking, stasis and inspissation of "vagal juice" lead to obstruction of acini and ducts, with pancreatic atrophy and fibrosis. Baggenstoss and his colleagues were able to extract secretin consistently from the mucosa of the upper part of the intestine in 30 persons between the ages of 2 months and 73 years. Their only failure was in a child with fibrocystic disease of the pancreas. This observation, although not conclusive, is highly suggestive. If it should prove correct, then fibrocystic disease represents a hormone deficiency state.

SUMMARY

Clinical and pathologic findings in a case of meconium ileus are presented. Meconium ileus represents the neonatal form of fibrocystic disease of the pancreas and is characterized clinically by intestinal obstruction. Theories explaining the pancreatic insufficiency are briefly reviewed.

Box 3531, Duke Hospital (Dr. Silverman).

News and Comment

ANNOUNCEMENTS

Continuation Course in Child Psychiatry.—A continuation course in child psychiatry for pediatricians and physicians will be presented at the Center for Continuation Study, University of Minnesota, Minneapolis, Nov. 27 to Dec. 1, 1950. Dr. Ralph D. Rabonovitch and Dr. John H. Waterman will participate as lecturers and group discussion leaders. Dr. Reynold A. Jensen, Head of the Child Psychiatry Service of the University of Minnesota, is in charge of the arrangements for the course and will also act as lecturer and group discussion leader.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

THERAPEUTIC RESULTS OF DIET OF CAROB BEANS IN INFANTILE ENTEROCOLITIS. ALVARO MASI, Riv. clin. pediat. **46**:27 (Jan.) 1948.

The author reports on the therapeutic results obtained in infants having acute and chronic enterocolitis with a diet based on carob beans (the seed of the locust tree, *ceratonia siliqua*).

FROM THE AUTHOR'S ABSTRACT.

CHOLINE IN THE THERAPY OF TOXICOSIS OF INFANTS. AUGUSTO GENTILI and WILLY TANGHERONI, Riv. clin. pediat. **46**:487 (Aug.) 1948.

The authors introduced the use of choline in the therapy of infantile toxicosis and report the good results obtained. It acts especially on the toxic component of this syndrome and makes the regression of the clinical symptoms more rapid. The authors are of the opinion that this method of treatment is of a great value in infantile toxicosis, owing to the protective action of choline on the liver.

FROM THE AUTHORS' SUMMARY.

Acute Infectious Diseases

TREATMENT OF LOCALIZED INFECTIONS WITH PENICILLIN INFILTRATION. FRANK K. INUI, Arch. Surg. **55**:58 (July) 1947.

Regional infiltration of localized infections with penicillin solution is a superior method of therapy. As much as 200,000 units can be infiltrated at any one time into the subcutaneous tissues about an infection without causing toxic reactions or sloughs. Total disability is greatly reduced with this method of therapy, and the deformities that result from surgical incision or excision are avoided. Inflammatory pain is quickly relieved after infiltration, and this relief is generally permanent after the first or second treatment. Infiltraton is moderately painful, but the pain does not last more than ten to twenty minutes if the penicillin solution contains 0.5 per cent procaine hydrochloride.

FROM THE AUTHOR'S SUMMARY.

TULAREMIA IN ILLINOIS. HERBERT E. MCDANIELS, Illinois M. J. **92**:224 (Oct.) 1947.

McDaniels reports that during the ten years ending in 1945, there was an average of about 185 reported cases of tularemia per year in Illinois. The annual number of cases ranged from 55 to 485. Reports for the years previous to 1932 are probably incomplete. Tularemia is reported from all sections of Illinois.

The range of ages in the reported cases is wide. The incubation period is three to four days. The duration of the disease in man varies from one to six months or longer. Ninety-five to 98 per cent of all infections are acquired from the skinning or cleaning of wild rabbits. A diagnosis may be made from the history, the lesions, a positive agglutination reaction, isolation of Pasteurella tularensis from the

lesions and a positive cutaneous reaction. An attack of tularemia leaves lasting immunity. The most effective treatment is with streptomycin.

BARBOUR, Peoria, Ill.

THE KNOWLEDGE OF HUMAN VIRUS INFECTIONS OF ANIMAL ORIGIN. K. F. MEYER and B. EDDIE, J. A. M. A. **133**:822 (March 22) 1947.

A summary of the characteristics of three virus diseases originating in animals is given because of the peculiar action of these agents on children.

Rabies is usually transmitted by a bite. Evidence disagrees concerning whether infected saliva can transmit the disease through the intact skin. Proper cleansing of the wound and observation of the biting animal are essential. With new vaccines, the incidence of postpasteurian myelitis has been reported to be as low as 0.07 per cent. Nationwide restraint and quarantine are necessary to control the disease. Annual vaccination of dogs is advisable until rabies has been eliminated from every state in the Union.

No evidence for a human strain of psittacosis (ornithosis) has been found, although the range of hosts among birds is great. Many human cases are diagnosed as "atypical pneumonia." Every patient with severe pneumonitis should be isolated to prevent spread. Diagnosis is made by isolation of the virus or by demonstration of a rise in the antibody titer. Treatment with a high dosage of penicillin given early in the disease and continued for several weeks seems to be effective.

Morbidity of western and eastern equine arthropod-borne virus encephalitis in endemic areas is highest in children under 5 years of age. Protection by vaccination may be obtained but no vaccines for human use are yet available. Methods of mosquito control are now being studied.

BAIRD, Wauwatosa, Wis.

OCULOGLANDULAR TULAREMIA TREATED WITH STREPTOMYCIN. PERCY MINDEN and J. E. SPRINGER, J. A. M. A. **134**:1061 (July 26) 1947.

A case of oculoglandular tularemia was presented, together with a brief review of the literature. This was an unusual manifestation of tularemia and probably the first to be treated with streptomycin. There was immediate and dramatic improvement of the primary lesion, constitutional symptoms and fever, but the general course of the disease, as manifested by a return of low grade fever, was prolonged for thirty days. During convalescence a second course of treatment with streptomycin brought about symptoms which probably represented either sensitivity of the patient to streptomycin or an impurity in the drug. The course of the disease was shorter in all respects than that of the average untreated attack.

FROM THE AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES IN MICE INFECTED WITH THE LARVAE OF ASCARIS LUMBRICOIDES: I. CRITERIA OF IMMUNITY AND IMMUNIZING EFFECT OF ISOLATED WORM TISSUES. J. F. A. SPRENT and H. H. CHEN, J. Infect. Dis. **84**:111 (March-April) 1949.

By the criteria devised, no immunity was consistently produced by active or passive immunization of mice with whole worm or with isolated tissues of the worm. These antigenic substances, therefore, are evidently not functional in immunity to infection. Inconclusive results were obtained by active and passive immunization with metabolic products of the worm.

TOOMEY, Cleveland.

THE ROLE OF THE SPLEEN AND LYMPHOID-MACROPHAGE SYSTEM IN THE QUININE TREATMENT OF GALLINACEUM MALARIA: III. THE ACTION OF QUININE AND OF IMMUNITY ON THE PARASITE. WILLIAM H. TALIAFERRO and LUCY GRAVES TALIAFERRO, J. Infect. Dis. **84**:187 (March-April) 1949.

The combined action of quinine and innate immunity or of quinine and innate and acquired immunity was studied by varying the time of quinine administration. This experimental attack led to the following results and conclusions:

During innate immunity in untreated normal and splenectomized chickens, the rate of reproduction was high, i. e., parasites grew and usually produced an average of 20 to 23 progeny more or less synchronously every thirty-six hours, but large numbers of parasites (about 40 per cent) died. This death was associated with phagocytosis by macrophages, especially in the spleen and liver.

When acquired immunity was superimposed on innate immunity in untreated normal and splenectomized chickens, the rate of reproduction was as high or almost as high as during innate immunity except temporarily at the parasitologic crisis, but even more parasites (90 to 99 per cent) died. This death was also associated with phagocytosis. Innate and acquired immunity, therefore, mainly acted on the parasites by killing them.

When quinine was given before infection, its antiplasmodial activity persisted as long as it remained in high concentrations in the blood. Thus, the acute rise of a test infection was delayed one day after 30 mg. of quinine per hundred grams of chicken was given by mouth five hours after 3 mg. per hundred grams of chicken was given intravenously and one-half an hour after 1.25 mg. per hundred grams of chicken was given intravenously. This last-mentioned amount given on three days was our so-called standard treatment. The activity of quinine was similarly demonstrated by a test superinfection. These data, as well as those on our experiment 6 and on various experiments by others, support the view that quinine acts directly on the parasite without metabolic transformation.

One larger intravenous dose was less effective for a shorter time, and three large intravenous doses (2.5 mg. per hundred grams of chicken) were more effective than the standard dose for about the same length of time. Quinine, therefore, mainly inhibited reproduction of the parasites.

These results do not substantiate the assumption that quinine is converted in vivo into a more active product or the further assumption that the drug makes the parasites more vulnerable to phagocytosis or to any other defense mechanism by inhibiting their reproduction. It is true that quinine inhibited reproduction of the parasites, but such parasites persisted abnormally long in the blood, hence they were not phagocytosed more avidly. FROM THE AUTHORS' SUMMARY.

STREPTOMYCIN IN THE TREATMENT OF SALMONELLA ENTERITIS IN INFANTS. SIDNEY ROSS, FREDERIC G. BURKE, E. CLARENCE RICE, HAROLD BISCHOFF and JOHN A. WASHINGTON, New England J. Med. **240**:602 (April 14) 1949.

The authors present 8 cases of salmonella enteritis in children treated with streptomycin. Three were given the drug orally alone as the syrup. Five received streptomycin both orally and intramuscularly, but combined therapy did not produce results superior to those obtained with oral administration alone. The results were not satisfactory, since only one child remained free of this pathogen, but failure could not be explained on the basis of either initial or acquired resistance to the drug.

WHEELOCK, Denver.

VACCINATION AS PRIMARY CONTACT WITH INFLUENZA A AND B VIRUSES. RAE V. NICHOLAS and WERNER HENLE, Pediatrics **3**:208 (Feb.) 1949.

A single dose of 0.5 cc. of commercially available influenza virus vaccine injected into children from 7 weeks to 3 years of age produced antibodies in about 70 per cent. Resulting antibody levels in the children, most of whom were born after the last widespread epidemics of influenza A and B, were distinctly lower than those observed in older persons who, in all likelihood, had experienced previous contacts with influenzal antigens. Two injections at a week's interval failed to result in a better antibody response in these children, in agreement with the experience gained in adults. An increase in the dose of vaccine appears unwarranted now, since the incidence of febrile reactions—all of short duration—exceeded 40 per cent. This inferior antibody response may be the result of several factors: (*a*) the smaller dose of vaccine that can be safely administered to such children; (*b*) the possibly inferior immune response of younger persons, and (*c*) the absence of a basic immunity to the antigens, present in most older persons as a result of previous contacts with influenzal viruses. Although it is impossible to decide among these factors, the booster effect of restimulation with small doses of antigen is a well known phenomenon in protective measures against other infectious agents. It is felt that such a mechanism may well be the explanation for the discrepancies between young children and older persons in their response to vaccination against influenza.

FROM THE AUTHORS' SUMMARY.

APICAL DIASTOLIC HEART SOUNDS IN ACTIVE RHEUMATIC FEVER. SIDNEY FRIEDMAN and T. N. HARRIS, Pediatrics **3**:603 (May) 1949.

In the course of a systematic clinical investigation of patients with active rheumatic fever, the interrelation between the apical diastolic third heart sound and the early diastolic murmur became so noticeable that a quantitative study of the relationship was undertaken. Of 400 patients with active rheumatic fever, 115, or 29 per cent, had on at least one occasion while under observation either a diastolic third heart sound or an early diastolic apical murmur. A total of 54 patients, or approximately half of those who showed either sound, demonstrated some sequence of the two sounds during the period of observation. The variations in this sequence are correlated with other evidence of progression or regression of the rheumatic process. Thus, the change from third heart sound to murmur occurred in 85 per cent of the instances among the acutely ill patients as compared with 30 per cent among patients in the convalescent phase, while the corresponding percentages for the reverse transition from murmur back to third heart sound were, respectively, 15 and 70. In each of the patients in whom an early diastolic murmur was heard at any time, there was also invariably present at the apex a blowing systolic murmur, indicating some degree of regurgitation at the mitral valve.

Some clinical and theoretic evidence for an interrelation between the third heart sound and the apical diastolic murmur in active rheumatic fever is presented, and the clinical evaluation of the third heart sound and the early murmur of carditis is discussed.

FROM THE AUTHORS' SUMMARY.

ENDEMIC CEREBRAL SYMPTOMS AND APHTHOUS STOMATITIS. W. GOUDSMIT, Nederl. tijdschr. v. geneesk. **93**:255 (Jan. 22) 1949.

In a small village 9 children became acutely ill with severe headache, some psychic deviations, drowsiness, vomiting, florid complexion and pain in the mouth

and throat. The greater number of the patients had distinct aphthous stomatitis. Two children were admitted to a neurologic clinic with the diagnosis of encephalitis; in only 1 of them did the cerebrospinal fluid show deviations. All the children recovered in the course of one week.

VAN CREVELD, Amsterdam, Netherlands.

Acute Contagious Diseases

ABSENCE OF SPASM DURING ONSET OF PARALYSIS IN ACUTE ANTERIOR POLIOMYELITIS. LEWIS J. POLLOCK AND OTHERS, Arch. Neurol. & Psychiat. **61**:288 (March) 1949.

In a study designed to demonstrate the presence of muscle spasm, as claimed by a group of poliomyelitis "experts," eleven neurologists were rotated in day and night watches at a hospital for persons with contagious diseases. All patients admitted with the diagnosis of poliomyelitis were examined on admission.

Thirty-two muscle groups were evaluated in each patient, and all patients were examined repeatedly during the stay in the hospital. A total of 30 patients was followed in this way for sufficient periods of time to allow an analysis. In no patient was there any indication of muscle spasm. It was concluded that spasm does not occur during the time of development of the paralysis.

McGURGAN, Evanston, Ill.

PROBABLE NASAL DIPHTHERIA, WITH OBSERVATIONS ON SCHICK TESTS. JOSEPH S. FEIBUSH, New York State J. Med. **47**:2600 (Dec. 1) 1947.

Feibush speaks of "the rising incidence of diphtheria noted by observers in Europe, Nova Scotia and upstate New York," and emphasizes "eternal vigilance" in holding this disease in check. The report concerns a 4½ year old boy with a purulent discharge from the left nostril and a thick, yellowish membrane extending from the floor of the nose up along the lateral wall. There was no fever. A culture was reported by the Health Department to be positive for diphtheria bacilli. Nasal cultures from the patient's father, mother and sister, made at intervals of approximately two weeks, were all negative. Penicillin was given locally by means of drops and nasal packs. A 12,500 unit dose of antitoxin was given intramuscularly. No foreign body was found. There was extension to the throat; a culture was positive for diphtheria bacilli. The author describes Schwarz's reported experiences with the Schick test, which were favorable. His own conclusions are that all children should have the Schick test and a control test three to six months after the last immunizing dose; if the reaction is positive, a course of secondary immunization with alum-precipitated diphtheria toxoid should be given, followed by the Schick test; a combined reaction should result in reimmunization without a Schick test; the Schick test should be repeated before the child enters school.

[ABSTRACTER'S NOTE.—It is not clear why the author uses the word "probable" in his report. The reported condition seems to be nasal diphtheria, with extension to the throat, as might have been expected. The author delayed for a month examination for a foreign body, which is important in all one-sided purulent nasal conditions, and especially in a case in which there is no fever.]

VOORHEES, New York [ARCH. OTOLARYNG.].

COMBINED IMMUNIZATION AGAINST DIPHTHERIA, TETANUS AND PERTUSSIS IN NEWBORN INFANTS: I. PRODUCTION OF ANTIBODIES IN EARLY INFANCY. PAUL A. DI SANT'AGNESE, Pediatrics **3**:20 (Jan.) 1949.

To determine the capacity of newborn infants to produce antibodies, 198 infants were inoculated against diphtheria, tetanus and whooping cough. A triple-combined vaccine containing aluminum hydroxide-adsorbed tetanus and diphtheria toxoids and 20,000,000,000 Hemophilus pertussis organisms per cubic centimeter was used. The first injection (0.5 cc.) was given at 7 days, the second (1 cc.) at 5 weeks and the third (1 cc.) at 9 weeks of age. A booster dose of triple-combined vaccine (0.5 cc.) was given between 6 and 12 months. Local and systemic reactions to 403 injections showed an increase in the number and severity of systemic reactions with subsequent injections; no such difference was observed in local reactions. Five sterile abscesses were noted among more than 500 injections, an incidence of about 1 per cent. No neurologic complications were observed.

More than half the newborn infants tested showed diphtheria antitoxin levels of 0.03 unit per cubic centimeter or more before inoculation. In 98 per cent of these tested at 1 week of age, agglutinins against H. pertussis could not be demonstrated. Fifteen per cent of newborn infants studied had detectable levels of tetanus antitoxin before prophylactic inoculation. One month after a third injection all infants tested had tetanus antitoxin levels of 0.1 unit per cubic centimeter or more ("protective level"), 92 per cent reaching "high" antitoxin levels of more than 1 unit per cubic centimeter. At this same age, 13 weeks, 84 per cent had diphtheria antitoxin levels of 0.03 unit per cubic centimeter or more ("protective level"). After the booster dose this percentage increased from 84 to 99 per cent.

One month after completion of inoculations about 60 per cent of the children had pertussis agglutinin levels considered "protective" (1:400). A booster dose failed to elicit any change in the number of patients with these high agglutinin titers. However, the booster dose caused a decrease in the percentage of infants showing an absence of pertussis agglutinins in the serum after the three initial injections. It is concluded that newborn infants do produce antibodies in response to antigenic stimuli. Response to the booster dose was further evidence of the immune status of most of these patients. FROM THE AUTHOR'S SUMMARY.

THE CHANGED STATUS OF DIPHTHERIA IMMUNITY. PHILIP COHEN, HERMAN SCHNECK, EMANUEL DUBOW and SIDNEY Q. COHLAND, Pediatrics **3**:630 (May) 1949.

Our studies and data indicate a considerable diminution of immunity to diphtheria during the past generation in New York city. The same seems to hold true for other sections of this country. While the increase of diphtheria morbidity has generally not been alarming in this country, we do not believe it wise or expedient to postpone the correction of this lost immunity until diphtheria assumes epidemic or threatening proportions. Since the soil may be prepared for the spread of diphtheria by loss of humoral immunity, a change in one of the other factors affecting the epidemiologic pattern of this disease may effect a sudden and serious increase in its occurrence. We have reestablished the validity of the Schick test as an index of humoral immunity by once more demonstrating its close correlation with an adequate antitoxin content of the blood. We stress the reliability of the Schick test since it is simple, easy to perform and interpret and always available.

We believe that the restoration of humoral immunity to diphtheria, and the excitation of cellular immunity by periodic stimulating inoculations, will cause a

decline in the susceptibility to and the morbidity of diphtheria. These ends can be attained by continuance of periodic recall doses at intervals of three to five years during childhood and early adult life, thus converting the potential protection of cellular immunity into the active protection of humoral immunity. In the case of women, it is wise to increase such immunity to an adequate level during pregnancy to safeguard the newborn with similarly adequate immunity.

FROM THE AUTHORS' SUMMARY.

PENICILLIN TREATMENT OF DIPHTHERIA CARRIERS. SAMUEL KARELITZ and VINCENT A. SPINELLI, Pediatrics **3**:639 (May) 1949.

The use of penicillin, 30,000 units injected intramuscularly every three hours and 1,000 units per cubic centimeters of isotonic sodium chloride solution administered in the form of nose drops every two hours during the day, effected a cure in 8 diphtheria carriers within thirty-six hours, in a ninth in five days and in 1 patient with faucial diphtheria. The diphtheria was of the mitis type in all. All organisms were resistant to a penicillin concentration of less than 0.5 units and many to 1 unit per cubic centimeter. Treatment was continued until five daily consecutive cultures yielded no organisms. After treatment five consecutive negative daily cultures were considered an indication of cure. It is believed that the parenteral therapy was important in the results. A single large dose of procaine penicillin is now being tried in an attempt to obviate the multiple injection technic.

FROM THE AUTHORS' SUMMARY.

PENICILLIN THERAPY OF DIPHTHERIA CARRIERS. JEROME T. Y. SHEN, Pediatrics **4**:188 (Aug.) 1949.

The problem of the diphtheria carrier and its importance in children are discussed. Nonpenicillin therapy of diphtheria carriers is briefly reviewed and commented on. Literature on penicillin treatment of the carriers is reviewed. An analysis of the results in 70 diphtheria carriers treated by different forms of penicillin therapy is presented and commented on, especially in regard to the correlation between the effectiveness of the therapy and the pathologic picture in the nose and throat. Rational treatment of diphtheria carriers is suggested in the conclusion of the paper.

FROM THE AUTHOR'S SUMMARY.

NON-PARALYTIC POLIOMYELITIS (SOME OBSERVATIONS ON DIFFERENTIAL DIAGNOSIS). NELLES SILVERTHORNE AND OTHERS, Canad. M. A. J. **66**:356 (April) 1949.

Studies on 37 patients suspected of having poliomyelitis were carried out during an epidemic. None of these had paralysis. About half were only mildly ill, and in the absence of an epidemic would not have been suspected of having poliomyelitis. Of the remainder, more severely ill, only 4 of 21 had an increase in spinal fluid protein persisting over several weeks. Seventy-five per cent of those with paralysis show such a rise. In only 4 of 20 patients was the virus isolated. The suggestion is made that there are other poliomyelitis-like virus infections which may occur concurrently with poliomyelitis. Cases should be diagnosed as nonparalytic poliomyelitis on clinical grounds until further studies are made.

McGUIGAN, Evanston, Ill.

LABORATORY STUDIES ON POLIOMYELITIS, TORONTO, 1947. A. J. RHODES AND OTHERS, Canad. M. A. J. **66**:359 (April) 1949.

Studies were carried out on 37 cases of supposed nonparalytic poliomyelitis. The virus was found in the stool in only 4 of 20 cases in which it was examined. Virus studies failed to confirm the diagnosis in 15 of 19 cases. The existence of a poliomyelitis-like illness is suggested.

McGUIGAN, Evanston, Ill.

AN EPIDEMIC OF POLIOMYELITIS IN AN INSTITUTION. T. GHIGLIAZZA, Lattante **19**:34 (Jan.) 1948.

In the provincial orphanage of Bergamo, Italy, an epidemic of poliomyelitis appeared during a period of twenty-six days in August and September 1947; there were 6 cases of the disease, all in infants between 7 and 14 months of age among a population of 66 infants. Ramon's diphtheria anatoxin was given to the rest of the children of the orphanage in the hope that it would have prophylactic value; after the anatoxin was given, only 1 other case developed.

HIGGINS, Boston.

EPIDEMIOLOGIC AND IMMUNOLOGIC ASPECTS OF TWO UNUSUAL CASES OF POLIOMYELITIS. S. BARBERI, Lattante **19**:65 (Feb.) 1948.

Two sisters, born nineteen months apart, each became ill, one at 30 days of age and the other at 20 days of age, with fever, hyperesthesia and muscular paralysis. The first child died within a few days of paralysis of the respiratory muscles and bronchopneumonia. The second child is living after two years but has flaccid paralysis of one arm and one leg. The possibility of some adult remaining as a carrier of the poliomyelitis virus over a period of nineteen months is considered.

HIGGINS, Boston.

FURTHER RESULTS FROM THE USE OF DIPHTHERIA ANATOXIN IN TREATMENT OF POLIOMYELITIS. T. GHIGLIAZZA, Lattante **19**:138 (March) 1948.

Over a period of eight years, 1938 to 1946, at the Maggiore Hospital, in Bergamo, Italy, 255 children in the acute phase of poliomyelitis were given 1 to 6 cc. of diphtheria anatoxin for its possible therapeutic value, as was suggested by Raffaelli. Of these, 71 (28 per cent) were reported as cured or greatly benefited, 127 as improved but having some residual paralysis and 57 as not benefited. In the author's opinion, this method of treatment has not proved superior to other methods, but he does express his belief that it is easy to apply during the acute stage of the disease and is not harmful.

HIGGINS, Boston.

A PARASITE-CONTAINING CELL IN THE PERIPHERAL BLOOD OF A SICILIAN CHILD WITH KALA-AZAR. PURRAZZELLA, Lattante **19**:290 (May) 1948.

In a Sicilian boy 16 months of age with kala-azar, a smear of the peripheral blood revealed a macrophage containing 47 Leishmania organisms.

HIGGINS, Boston.

POLIOMYELITIS IN THE PROVINCE OF BRESCIA, ITALY, 1936 TO 1946. A. PAGANI-CESA and G. C. ABBA, Lattante **19**:321 (June) 1948.

An epidemiologic study of the 605 cases of poliomyelitis occurring in the province of Brescia, Italy, between 1936 and 1946 was made, particular attention being paid

to the geographic location of the home and to the economic status of the family. The authors decided that the data obtained permitted of no definite conclusion.

HIGGINS, Boston.

VARIATIONS IN CREATINE FRACTIONS OF BLOOD AND URINE AFTER PHYSICAL EXERCISE IN PATIENTS WITH POLIOMYELITIS. TERESA CAPECCHI, Pediatria **56**:64 (Jan.-March) 1948.

The influence of physical exercise on the blood and urinary creatine fractions in children with paralysis following poliomyelitis, in children with myopathic disorders and in control children was studied. At rest, compared with the controls, in the children with poliomyelitis and in those with myopathies the blood creatine showed higher values and the creatinine remained almost the same; the creatinuria was far higher and the creatininuria lower. After light physical exercise, the twenty-four hours urine of 20 poliomyelitic children showed the creatine to be increased in only 6. It was consistently elevated in 3 of the myopathic subjects; the creatinine content was often diminished. The controls showed no changes. After heavier exercise in 25 poliomyelitic children, the creatinemia was elevated in 16 and the creatininemia unaltered; creatinuria appeared in 3 subjects after exercise and the preexistent creatinuria was increased in 20. The behavior of creatinine is variable. The 2 subjects with progressive muscular dystrophy showed a prolonged increase in blood and urinary creatine; the creatinine was nearly always unaltered. Among 3 controls, the test resulted in increase of creatinuria in only 1 of the subjects.

The evidence reveals that in children with poliomyelitis intensive work sensibly modifies the creatine fractions, which remain almost unaltered by light work. It indicates that the kinesitherapy of these patients tiredness ought to be avoided, in order not to provoke a disturbance of the muscular biochemical balance with further damage to the muscle itself.

FROM THE AUTHOR'S SUMMARY.

MEASLES DURING PREGNANCY AND CONGENITAL CATARACT OF THE NEWBORN ACCOMPANIED WITH A DIGITO-OCULAR PHENOMENON. A. FRANCESCHETTI, Ophthalmologica **114**:332 (Oct.-Nov.) 1947.

The author noted rubbing of the eyes with the fingers in children with congenital cataract due to measles, particularly in poor illumination, and in infants with complete cataract. The author recommends discission as soon as possible, before nystagmus develops. He offers in explanation of the etiology the fact that the measles virus is ectodermotropic and therefore attacks the lens.

KIRBER [ARCH. OPHTH.].

OBSERVATIONS MADE IN FOLLOW-UP EXAMINATIONS OF POLIOMYELITIS PATIENTS. ARVO ARVOLA, Ann. med. int. Fenniae **36**:211, 1947.

Ninety of one hundred and seventeen patients with paretic poliomyelitis treated at the City Hospital for Infectious Diseases, Helsinki, Finland, from 1937 to 1942 were reexamined in 1946. It was found that 17 per cent of the patients had recovered completely; more than 40 per cent were practically healthy (less than 10 per cent disability); about 60 per cent displayed only slight defects (less than 30 per cent disability), and 14 per cent were seriously disabled (over 70 per cent disability). Eighty per cent of the persons over 18 years of age were able to

support themselves. Adults contract the disease as often as children, but the attack is severer. The mortality rate is highest in the adult group (32 per cent) and lowest in children below 7 years old (0 per cent).

WALLGREN, Stockholm, Sweden.

IMMUNIZATION AGAINST SCARLET FEVER AND RETURN CASES 1937-1945. AIMO OJALA, Ann. med. int. Fenniae **36**:308, 1947.

The object of the study was to determine whether the occurrence of return cases can be decreased by protective immunization of the members of the family of the discharged patient. During the vaccination period 1940 to 1945 the families of 2,489 patients with scarlet fever were vaccinated with Gabritchewski's vaccine (364 persons), Faragó's vaccine (117 persons) or "Scharlach-Adsorbat-Impfstoff" (830 persons). A new attack of scarlet fever in the family within eighteen days after the patient is discharged was considered a return case, provided there was no other possibility of infection. The control group consisted of 2,180 patients who had scarlet fever from 1937 to 1939. The rate of return cases was 2.1 per cent in the vaccinated group and 3.4 per cent in the control group. The lowest rate was in those vaccinated with Faragó's vaccine and "Scharlach-Adsorbat-Impfstoff" (1.1 and 1.3 per cent, respectively).

WALLGREN, Stockholm, Sweden.

ON CHANGES IN THE CEREBROSPINAL FLUID DURING MEASLES. AIMO OJALA, Ann. med. int. Fenniae **36**:321, 1947.

The spinal fluid was examined in 123 unselected patients with measles and in 4 with signs of encephalitis. Pleocytosis was observed in 46 patients; in 25 the count was more than 5 cells, in 15 more than 10 cells and in 5 more than 50 cells per cubic millimeter. Of 16 patients with pulmonary complications 2 had pleocytosis. The pleocytosis usually appeared on the fifth to the tenth days of the rash. The pleocytosis can attain such a high degree (a maximum of 758 cells) that the fluid is turbid even though the patient has no clinical signs of involvement of the central nervous system. There was no relation between the duration of fever and exanthem and the appearance of pleocytosis.

WALLGREN, Stockholm, Sweden.

Chronic Infectious Diseases

THE QUANTITATIVE TUBERCULIN TEST. C. EUGENE WOODRUFF, Am. Rev. Tuberc. **55**:488 (June) 1948.

In view of the increasing reliance being placed on the roentgenogram as a diagnostic measure in surveys for tuberculosis, Woodruff emphasizes the necessity for checking roentgenologic findings with the reaction to the tuberculin test before a definite diagnosis of tuberculosis is made. The procedure used in the observations on which this paper is based was a first test with 0.1 cc. of a 1:10,000 dilution of old tuberculin intracutaneously, followed in forty-eight hours, if the reaction was negative, with 1:1,000 dilution of old tuberculin and, if still negative, in forty-eight hours more with 1:10 dilution of old tuberculin. An area of induration or edema 5 mm. or more in diameter was considered a positive reaction. Those who failed to react to the 1:10 dilution of old tuberculin were considered anergic.

The differential diagnosis in subjects with roentgenographic appearance suggestive of tuberculosis who fail to react to high concentrations of tuberculin is simplified by the knowledge that the patient with active tuberculosis is always critically ill. Conversely, if the subject is not acutely ill, he is probably nontuberculous in spite of the roentgenologic findings. This is also substantiated by the laboratory findings, as tubercle bacilli are never observed in the sputum of an anergic patient unless he is critically ill. The anergic tuberculous patient is much more likely to have large numbers of tubercle bacilli in his sputum than is the highly allergic patient. For these reasons, a plea is made for a more effective use of that old tool, the tuberculin test.

SMITH, Ogden, Utah.

THE USE OF MICE IN EXPERIMENTAL CHEMOTHERAPY OF TUBERCULOSIS. GUY P. YOUMANS and GORDON W. RALEIGH, J. Infect. Dis. **82**:221 (May-June) 1948.

Twenty compounds were tested for their ability to suppress experimental tuberculosis in mice. Only streptomycin and paraaminosalicylic acid were found to be appreciably effective.

The value of histopathologic examination in the detection and evaluation of the activity of antituberculosis drugs in mice is discussed.

TOOMEY, Cleveland.

MULTIPLE CYST-LIKE OSSEOUS TUBERCULOSIS IN CHILDREN. SEDDIK A. NAGA, J. Roy. Egyptian M. A. **31**:245 (March) 1948.

A case is described of an 18 month old child with more than thirty separate cystic foci of tuberculous infection spread over the long bones of the skeleton, the digits of the hands and feet and the ribs. The child had primary tuberculosis of the lung and tuberculous adenopathy.

MCGUIGAN, Evanston.

STREPTOMYCIN IN TREATMENT OF MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS IN CHILDHOOD. GIROLAMO TACCONE, Pediatria **56**:1 (Jan.-March) 1948.

The author, after recounting the proofs of the efficiency of streptomycin in tuberculous diseases, reports on 13 patients with miliary tuberculosis and on 11 with tuberculous meningitis who were treated with streptomycin, which he considers to be, at present, the remedy of choice for these two diseases.

He enlightens the reader on the possibilities of improvement in the patients treated and the modifications which streptomycin therapy causes in the evolution of the disease. His series shows 3 apparent recoveries from miliary tuberculosis, from the clinical and roentgenologic points of view. Frequent symptomatic remissions occurred in his patients with tuberculous meningitis, and in 1 patient complete regression of clinical (not humoral) symptoms resulted. However, two relapses occurred in this patient which were successfully checked by intradural administration of streptomycin.

FROM THE AUTHOR'S SUMMARY.

IMPORTANCE OF EARLY STREPTOMYCIN THERAPY IN CASES OF TUBERCULOUS MENINGITIS. G. RICCI, Pediatria **56**:211 (April) 1948.

One hundred and five patients with tuberculous meningitis were treated with streptomycin in the clinic for infectious diseases in Rome, Italy, during the fourteen month period from January 1947 to March 1948. Fifty-seven patients died; 44 are still living, and from 4 no report could be obtained concerning their status.

Six have now been living over ten months. Of the last 25 patients, only 1 died within the first fifteen days after admission to the hospital. The detection of cases of tuberculous meningitis before severe damage to the central nervous system has occurred and the institution of immediate treatment pave the way for complete recovery.

HIGGINS, Boston.

HEPATIC FUNCTION IN CHILDHOOD TUBERCULOSIS. V. BAFFI and CARMINE MELINO, Pediatria **56**:229 (April) 1948.

Hepatic function was estimated by various methods in 64 children with tuberculosis. Hepatic function is damaged more by toxicity in the tuberculous patient than by the extent of the lesions.

HIGGINS, Boston.

HEMOPOIETIC ACTIVITY OF BONE MARROW IN CONGENITAL SYPHILIS. G. TONIOLO, Pediatria **56**:279 (April) 1948.

Bone marrow smears of 9 infants and 1 older child with congenital syphilis were studied. The maturation of the cells of the white blood cell series was retarded, more immature cells, especially of the eosinophil type, usually being present. Slow maturation was also present in the red blood cell series, stippled cells often being noticeable. The megakaryocytes were more plentiful in the children in whom the number of eosinophil cells was increased.

HIGGINS, Boston.

TUBERCULOUS MENINGITIS AND STREPTOMYCIN. J. BRDLIK, Pediat. listy **3**:1 (Jan.) 1948.

For the correct diagnosis of tuberculous meningitis the author stresses the necessity for proof of tubercle bacilli in the cerebrospinal fluid, a positive result on culture and a positive reaction in the guinea pig. He describes in detail a case of tuberculous meningitis treated almost exclusively by injections of streptomycin in doses of 1 Gm. daily from the eleventh day of the illness. The total amount of 90,000,000 units was given intramuscularly (except for 1 dose of 125,000 units which was administered intrathecally) within ninety days. The state of health of the boy, seven months after the onset of the treatment, was excellent. The initial ptosis of the right eyelid had disappeared; vision and hearing were intact; only paresis of the ocular muscles persisted and there were slight inflammatory changes in the cerebrospinal fluid. The author discusses 11 further cases in which the final result cannot yet be told. He is of the opinion that in the future the intramuscular application of streptomycin in the treatment of tuberculous meningitis will gain preference.

FROM THE AUTHOR'S SUMMARY.

TUBERCULOUS MENINGITIS CURED WITH STREPTOMYCIN. JUAN R. DÍAZ NIELSEN, Arch. argent. de pediat. **29**:85 (March) 1948.

A 5 year old boy had nonsuppurative meningitis. The author reviews the different types of meningitis within the meningeal syndrome and makes the differential diagnosis between choriomeningitis and tuberculous meningitis. Treatment with streptomycin was started the day the meningeal signs were first noted. This was possible because the infected child was already under observation. The intramuscular injections were well tolerated except for some swelling of the region, which was alleviated with application of hot pads. Diluted procaine hydrochloride applied before the streptomycin injections also gave local relief. The intratracheal

injections of the drug diluted in saline solution were tolerated just as well. The patient received 207 Gm. of streptomycin intramuscularly during five months of treatment, and 3 Gm. intratracheally during about one and a half months. Improvement was first noted on approximately the twenty-fifth day of treatment. Rigidity and photophobia were the first symptoms to disappear. The author is of the opinion that the drug is efficacious in the treatment of tuberculous meningitis, although it does not affect the adenopathy.

ROJAS, Boston.

TREATMENT OF CONGENITAL SYPHILIS WITH PENICILLIN. J. I. DE BRUYNE, Nederl. tijdschr. v. geneesk. **92**:1454 (May 15) 1948.

Ten infants with congenital syphilis were treated with penicillin in dosages of 150,000 units per kilogram of body weight. They were all less than 4 months old when the treatment began. The total control period varied from six to fifteen months. In 8 children a good result was obtained: The clinical and roentgenologic symptoms disappeared, and in 7 of these children the serologic reactions became negative within four months after the treatment had started. In 1 of the children the Kahn reaction was still positive after eight months, but the titer had diminished. These favorable results were ascribed to the fact that the children could be treated in the first months after birth. One child, however, died shortly after the beginning of treatment with penicillin. The patient, although not particularly severely ill, had an elevated temperature six hours after the first injection of penicillin and died the next day with hyperpyrexia. Another child died suddenly in a convulsion one month after the treatment had been completed, so that no direct connection between the child's death and the treatment could be concluded.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF CONGENITAL SYPHILIS. R. KOOIJ, Nederl. tijdschr. v. geneesk. **93**:1461 (May 15) 1948.

Congenital syphilis was a rare disease in the Netherlands before the occupation. In the venereologic department of the University of Amsterdam, Netherlands, only 3 children were treated between 1938 and 1943, whereas in the next four years 35 syphilitic children were treated in the clinic.

Of 25 mothers, 8 were not treated at all before the child's birth, and the other 17 mothers had had insufficient treatment. The treatment of the children varied with the circumstances of the latter years of the war: 10 children were treated with acetarsone (spirocid*) during several periods. Others received injections of bismuth, sulfarsphenamine (belasphin) or acetylarsan (diethylamine acetarsone), whereas, when penicillin became obtainable, 7 patients were treated with 100,000 to 125,000 units of penicillin per kilogram of body weight. As the other antisyphilitic agents must be given in several courses in order to obtain good results, one should not give only one course of penicillin. Perhaps the best treatment of congenital syphilis is use of penicillin combined with other antisyphilitic agents.

VAN CREVELD, Amsterdam, Netherlands.

BCG VACCINATION. T. BAUMANN, Schweiz. med. Wchnschr. **78**:317 (April 10) 1948.

The author reviews the results of BCG vaccination and gives the opinions of those advocating its use in foreign lands. He recommends that it be introduced into Switzerland. He is of the opinion that possibly in the next decade a remedy may be found to be used against early infections. In that case BCG would be

unnecessary. He states, however, that the BCG vaccination should be employed in those who are particularly exposed to primary infections, including infants, newborn and small children up to the fifth year of age and also persons in the puberal period, 14 to 25 years of age. Nurses and attendants on the sick, students of medicine and veterinary medicine, laboratory assistants and those who work in roentgenologic laboratories should be included in the group to be immunized with BCG. He recalls the directions of Wallgren, namely, that all candidates for the vaccination should be tested with tuberculin before and after the vaccination and that immunized persons should not be exposed to the infection until the symptoms of allergy are apparent.

ABT and ABT, Chicago.

TWENTY YEARS OF BCG VACCINATION IN SWEDEN. ARVID WALLGREN, Ann. paediat. **170**:57 (Feb.) 1948.

The type of BCG vaccination introduced in 1927 in Sweden was used afterward in that country and in other countries. The BCG vaccine is injected intradermally. In order to prevent persons already infected with tuberculosis from being inoculated, a negative tuberculin reaction is required prior to the vaccination. After the inoculation, it is necessary to protect the vaccinated person against virulent infection about six to eight weeks, until tuberculin allergy can be demonstrated. The dose used for inoculation during the past twenty years was invariably 0.5 mg. Up to Jan. 1, 1947, more than 500,000 persons were vaccinated in Sweden, and the frequency of the vaccination is gradually increasing, so that during 1947 probably more than 250,000 persons were vaccinated. Until now no serious complications have occurred, and there are no signs that the BCG bacilli have regained their original virulence. The only disadvantage connected with the vaccination is, in rare cases, formation of an abscess in the site of injection. These abscesses are rarely larger than a hazelnut and they heal spontaneously in a few months. The immunity produced by the vaccination has an individually different duration but lasts, as a rule, five to ten years. The result of the vaccination was satisfactory in Sweden, and the vaccination has become an important factor in the fight against tuberculosis. The BCG vaccination appears to give excellent protection against the immediate results of a virulent primary infection, i. e., against clinical primary tuberculosis, miliary tuberculosis and tuberculous meningitis and, to a certain extent, also against pleurisy and pulmonary tuberculosis with cavity formation so far as it is the sequel of a fresh primary tuberculosis of the lung. On the other hand, not much can be expected from BCG vaccination as a prophylactic measure against late secondary tuberculous conditions, such as skeletal tuberculosis, renal tuberculosis and ordinary phthisis.

FROM THE AUTHOR'S SUMMARY.

FAMILIAL NUCLEAR ANOMALY OF THE LEUKOCYTES, AFTER PELGER-HUËT. E. KOELEWYN and D. P. R. KEIZER, Nederl. Tijdschr. v. geneesk. **92**:4022 (Dec. 4) 1948.

A boy 8 years of age showed a nuclear anomaly of the leukocytes similar to that reported by Pelger-Huët, with a normal leukocyte count, normal sedimentation rate of the erythrocytes, strong shift to the left and 21 per cent stab forms; the polymorphonuclear cells had one or two fragments with a peculiar structure in the nucleus and large granules. The stab cells had a short, broad nucleus with an odd structure. The bone marrow had no distinct deviations, with the exception of the same nuclear anomalies of the polymorphonuclear and stab cells of the blood.

This nuclear anomaly is dominant hereditarily and not sex bound. The mother of this patient, her brother and her half-brother also had this anomaly. The frequency of abortion and death at an early age was striking in this family: The patient's mother had 3 abortions and 1 stillborn child. Her brother's wife had 1 abortion and 1 normal child. The half-brother begot 2 abortions and 1 child with the aforementioned anomaly.

In rabbits this disease also occurs. In the cross breeding experiments of Undritz, Nachtheim and others, it appeared that in these animals abortion was frequent, while the few surviving young animals showed retardation in growth and anomalies of the skeleton.

From these facts it may be concluded that the anomaly of Pelger-Huët is probably combined with other undesirable hereditary traits.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Blood, Heart and Blood Vessels and Spleen

COARCTATION AND ANEURYSM OF THE AORTA. HARRIS B. SHUMACKER JR., Ann. Surg. **127**:635 (April) 1948.

A case report is presented of coarctation of the aorta complicated by a saccular aneurysm distal to the coarctation and by bacteremia. The bacteremia was treated successfully, and the coarctation and aneurysm were subsequently excised, with repair of the aorta by end to end suture.

The author reports the case in detail and is of the opinion that no similar instance of successful extirpation of an aortic aneurysm by excision and resuture of the divided aorta has ever been reported.

BANTIN, Omaha.

THE SURGICAL TREATMENT OF THE INFANTILE TYPE OF COARCTATION OF THE AORTA. JULIAN JOHNSON and CHARLES K. KIRBY, Ann. Surg. **127**:1119 (June) 1948.

Three patients (aged 13, 17 and 20 years) with the infantile type of coarctation of the aorta were operated on. In 2 patients the subclavian artery was divided and rotated downward to bridge the defect by an end to end anastomosis with the descending aorta. In the third patient the operation had to be abandoned because of the atheromatous condition of the vessel walls.

The authors are of the opinion that the use of the subclavian artery to bridge the gap in the infantile type of coarctation of the aorta is worthy of further trial in selected cases.

BANTIN, Omaha.

A DEPENDABLE METHOD FOR CONSTANT INTRAVENOUS THERAPY IN INFANTS USING POLYETHYLENE TUBING. EBEN ALEXANDER JR., WILFRED SMALL and JAMES B. CAMPBELL, Ann. Surg. **127**:1212 (June) 1948.

Major surgical procedures in infants and small children present many special problems, not the least of which is the technical difficulty of administering fluids and blood intravenously. The loss of 100 cc. of blood in a small infant during an operation may be unavoidable. However, it represents a significant percentage of the blood volume of a small infant and must be quickly replaced.

The authors present in detail their technic for administration of fluids and blood intravenously to small infants. Use is made of a new polyethylene plastic tubing. This tubing is flexible, semitransparent, tough, light, easily sterilized and nonirritating to the tissues. The tubing is usually inserted into the medial melleolar vein. The method is dependable and easily employed, even by inexperienced persons.

It has been the usual practice to remove the tubing from the vein within 24 hours or more, and in 1 instance it was allowed to drip continuously for five days.

Superficial phlebitis occasionally develops, but in only 1 case did it occur when the tubing had been in place less than 24 hours and in only 5 cases in less than 48 hours.

BANTIN, Omaha.

A CAUSE FOR THE REESTABLISHMENT OF COMMUNICATION FOLLOWING LIGATION OF PATENT DUCTUS ARTERIOSUS. CLARENCE E. REES, California Med. **68**:35 (Jan.) 1948.

A case of a 7 year old girl is reported in which the reestablishment of communication following ligation of a patent ductus arteriosus was observed to be due to detachment of the ductus from the aorta and pulmonary artery at the points of junction with these vessels. Two possible explanations for this detachment are suggested.

PRYOR, Redwood City, Calif.

TREATMENT OF METHEMOGLOBINEMIA. OSCAR BODANSKY and HELMUT GUTMANN, J. Pharmacol. & Exper. Therap. **90**:46 (May) 1947.

There are numerous reports of the successful treatment of methemoglobinemia in man by the intravenous use of methylene blue and, in fewer cases, of ascorbic acid. The authors experimented with dogs to determine the effective dosage of remedies at the various levels of methemoglobinemia. Their summary gives a satisfactory understanding of the results:

The minimal lethal level of para-aminopropiophenone-induced methemoglobinemia in dogs is about 80 to 85 per cent of the total blood pigment.

At very high but nonlethal levels, methemoglobinemia is reduced much more rapidly by methylene blue than by ascorbic acid or by BAL (2,3-dimercaptopropanol). At a dose of 1 mg. per kilogram of body weight intravenously methylene blue is highly and rapidly effective in saving dogs from death at degrees of methemoglobinemia which would otherwise be fatal.

A correlation of the clinical literature with the experimental results obtained in the present study indicates that the minimal lethal level of methemoglobinemia in man approaches that in the dog and that a dose of 1 to 2 mg. of methylene blue per kilogram of body weight is highly and rapidly effective in counteracting the symptoms of severe methemoglobinemia.

PILCHER, Cleveland.

BAL INHIBITION OF MERCURIAL DIURESIS IN CONGESTIVE HEART FAILURE. RALPH M. SUSSMAN and JEROME A. SCHACK, Proc. Soc. Exper. Biol. & Med. **66**:247 (Oct.) 1947.

Seven patients with chronic congestive heart failure (5 with hypertensive arteriosclerotic type, 1 with the rheumatic type and the other with a disorder of undetermined origin) were studied to determine whether BAL (2,3-dimercaptopropanol or British antilewisite) influenced the effectiveness of mercurial diuretics. Meralluride "mercuhydrin" sodium, which contains 39 mg. of mercury in organic combination with 48 mg. of theophylline U. S. P. per cubic centimeter of aqueous solution, was the mercury preparation employed. The patients were kept under standard conditions for persons with cardiac disease, with partial rest in bed, salt-poor diet, no fluid restriction and in most instances some digitalis therapy. BAL in oil (10 per cent solution of 2,3-dimercaptopropanol in benzyl benzoate and peanut oil) was given for a period of twenty-four to thirty-six hours, 2.5 mg. per

kilogram of body weight every six hours intramuscularly. Meralluride sodium was then given intramuscularly in 2 cc. doses. The individual loss of weight in forty-eight hours after administration of the mercurial drug alone was between 2¾ and 5½ pounds (1,247 and 2,381 Gm.). Patients receiving BAL in addition in most instances gained only 2 pounds (907 Gm.) or lost ½ pound (227 Gm.) or less. It is concluded that use of BAL in oil completely annuls the diuretic effect of the organic mercurial compound known as meralluride. It was observed that administration of BAL in oil intensified the preexisting hypertension in the presence of heart failure. Treatment with procaine hydrochloride in addition to BAL in oil did not affect the antidiuretic action.

HANSEN, Galveston, Texas.

INCIDENCE OF RH FACTOR AMONG THE INDIANS OF THE SOUTHWEST. EARL B. GERHEIM, Proc. Soc. Exper. Biol. & Med. **66**:419 (Nov.) 1947.

Indians who were patients at the United States Indian Hospital and Indian School Hospital at Albuquerque, N. Mex., and students at the Indian Day School at Albuquerque and the Day School at Isleta, N. Mex., were studied for Rh factor. The age range was from school age to 60 years. In the group of full-blooded (4/4) Indians studied 385 were Rh positive and 1 was Rh negative.

HANSEN, Galveston, Texas.

ANEMIA IN RATS INFESTED WITH BARTONELLA MURIS AND INJECTED WITH PTEROYLGLUTAMIC ACID. HILDA A. SMITH and FREDERICK E. EMERY, Proc. Soc. Exper. Biol. & Med. **67**:178 (Feb.) 1948.

Rats on a standard diet were given intraperitoneal injections of saline solution containing blood taken from rats having an acute infection with Bartonella muris. Some of the rats in each group were given daily intramuscular injections of 40 micrograms of folic (pteroylglutamic) acid. The means (for 20 animals in each group) when charted for curves of the number of red cells and the hemoglobin concentration showed little difference for about eighteen days. In other words, there is a progressive anemia apparently caused by the Bartonella infection. The regeneration of blood exceeded the breakdown of red cells, however, in the animals given the folic acid. The same difference held in the animals which were splenectomized and given injections of folic acid. Curves made from the data presented on the animals treated showed that they were much less anemic than the control animal for thirty-five days or longer. HANSEN, Galveston, Texas.

PENICILLIN, STREPTOMYCIN, DICUMAROL AND BLOOD COAGULATION: THROMBOPLASTIC PROPERTIES OF PENICILLIN. DAVID I. MACHT, South. M. J. **41**:720 (Aug.) 1948.

Laboratory studies have shown that penicillin shortens the coagulation time of whole blood, as well as the prothrombin time. This has been demonstrated to be true in human subjects as well. Amorphous penicillin seems to be more effective than the crystalline preparation because the various penicillin fractions differ in their thromboplastic strength. The author states that the thromboplastic effects of penicillin and the anticoagulant effects of dicumarol are mutually antagonistic.

LOGAN, Rochester, Minn.

SURGICAL TREATMENT OF CONGENITAL HEART DISEASE. G. MURRAY, Canad. M. A. J. **58**:10 (Jan.) 1948.

A brief discussion of congenital heart disease is given. Surgical treatment was given in 62 cases, including 41 of tetralogy of Fallot, 12 of patent ductus arteriosus and 9 others. Over-all mortality was 11.3 per cent, with only 7.3 per cent among the cases of tetralogy of Fallot, in which operation was by Blalock's technic.

McGUIGAN, Evanston, Ill.

A CARDIAC ANOMALY. B. I. LEWIS, Canad. M. A. J. **58**:186 (Feb.) 1948.

A case of complete transposition of the great vessels, with patent foramen ovale, is presented. The Spitzer "detorsion theory" of the causation of such defects is discussed.

McGUIGAN, Evanston, Ill.

INFECTIOUS MONONUCLEOSIS COMPLICATED BY THROMBOCYTOPENIC PURPURA. A. GOLDBLOOM and R. DENTON, Canad. M. A. J. **58**:189 (Feb.) 1948.

Thrombopenic purpura as a complication of infectious mononucleosis is described. Recovery was spontaneous without splenectomy. The importance of differentiating this disease picture from that of leukemia is stressed.

McGUIGAN, Evanston, Ill.

DIAGNOSIS OF CONGENITAL HEART DISEASE. J. D. KEITH, Canad. M. A. J. **58**:247 (March) 1948.

Common types of congenital heart disease are discussed and the cardinal diagnostic points outlined. Use of the intracardiac catheter and angiocardiography are described. Accurate diagnosis is especially important now because of the extending field of cardiac surgery.

McGUIGAN, Evanston, Ill.

METHEMOGLOBINEMIA IN AN INFANT. N. GOLUBOFF, Canad. M. A. J. **58**:601 (June) 1948.

A case of methemoglobinemia due to nitrate in well water is described. Attention is called to the factor of contamination by animal excreta and organic waste in the production of high nitrate content in the water of poorly placed wells.

McGUIGAN, Evanston, Ill.

INTRACARDIAC CATHETERIZATION IN INTERAURICULAR SEPTAL DEFECTS. A. W. BANGHART and J. A. LEWIS, Canad. M. A. J. **58**:605 (June) 1948.

Intracardiac catheterization may be of important help in the diagnosis of interauricular septal defects by the detection of a higher oxygen saturation in the right atrial blood than in the caval blood in the absence of tricuspid insufficiency.

McGUIGAN, Evanston, Ill.

PERSISTENT DUCTUS ARTERIOSUS CORRECTED BY OPERATION. DE VERNEJOUL, P. GIRAUD, METRAS and PIERRON, Presse méd. **56**:242 (March 31) 1948.

The correction of this congenital defect has rarely been recorded in France. The authors present a typical case occurring in a girl 6 years of age, with a favorable outcome following operation. They present the diagnostic findings and the surgical indications and discuss the prognosis.

DAFFINEE, Melrose, Mass.

CONGENITAL (NEONATAL) THROMBOPENIA. ROBERT F. LANDOLT, Helvet. paediat. acta **3**:3 (Feb.) 1948.

From the Children's Hospital in Zurich, Switzerland, 2 cases of proved congenital thrombopenia are reported. Case 1 was a rapid, transitory nonfamilial form. Shortly after birth a cranial injury obviously due to hemorrhagic diathesis was manifested; the infant became an imbecile.

Case 2 was that of a poorly thriving, prematurely born infant exhibiting a nonfamilial thrombopenia of prolonged, alternating intensity. Initially, there was complete absence of megakaryocytes in the bone marrow. Then for a short period these could be observed. However, they were often small and atypical in form. The infant died, the clinical picture representing hyperpyrexia. It was noteworthy that the thrombopenia was associated with various malformations (palatoschisis; cake kidney).

Three forms of congenital thrombopenia were distinguished:

1. Congenital thrombopenia associated with purpura of the mother. An account of a third special case belonging to this most frequent form of the disease is given. Earlier the mother had had thrombopenic purpura. In response to the administration of quinine during delivery, petechiae and severe hemorrhage appeared. The infant likewise showed cutaneous bleeding and a hemorrhage of the vitreous humor which led to blindness of the right eye. Since no hematologic investigations were carried out shortly after birth, it cannot be said with certainty that this was a case of thrombopenia.

2. Congenital thrombopenia of a transitory type without familial taint (case 1).

3. Congenital hypoplastic thrombopenia with a poor prognosis, associated with other malformations (case 2).

FROM THE AUTHOR'S SUMMARY.

SUBACUTE, RECURRING HEMOPTYSIS IN HEMORRHAGIC THROMBOPENIC DIATHESIS. C. FREIRE and M. CORDEIRO, Helvet. paediat. acta **3**:255 (Sept.) 1948.

Thrombopenic purpura (Werlhof's disease) occurred in a boy 6 years of age. The first and main symptom was a subacute, recurrent hemoptysis, the roentgenogram showing hemosiderosis of the lungs. For fear of brown induration of the lungs, splenectomy was performed and was completely successful. Some months after the operation, the child showed complete recovery; he had no further signs of anemia, thrombopenia or hemoptysis. His general condition was good, and a series of roentgenograms taken after the operation showed the gradual but complete regression of the pulmonary alterations.

FROM THE AUTHORS' SUMMARY.

TREATMENT WITH FOLIC ACID IN PERNICIOUS FORMS OF GOAT'S MILK ANEMIA. CONRAD GASSER, Helvet. paediat. acta **3**:301 (Sept.) 1948.

Treatment with folic acid was successful in an infant, 3 months old, with severe familial goat's milk anemia, which was normochromic and megalocytic and combined with thrombopenia. Within a week the hypercellular megaloblastic marrow matured and a normoblastic and reticulocytic crisis followed, first in the marrow and then in the blood. The erythrocyte volume sank to normal. At the same time the high iron and bilirubin levels dropped, while the albumin, cholesterol and copper levels rose. Within three weeks the anemia was cured, and an examination six months later showed no pathologic signs apart from an increased lymphocyte count in the bone marrow.

The effects of folic acid on the bone marrow, blood picture and blood chemistry were carefully followed and charted.

FROM THE AUTHOR'S SUMMARY.

MALIGNANT ACUTE FORM OF GAUCHER'S DISEASE. R. F. LANDOLT, H. U. ZOLLINGER and C. H. EUGSTER, Helvet. paediat. acta **3**:319 (Sept.) 1948.

A rare case of acute malignant Gaucher's disease occurred in a 7 month old infant. The most striking clinical symptoms were laryngeal spasms, apnea and cyanosis, together with notable underdevelopment and gross hepatosplenomegaly. The pathologic examination, and particularly the phase-contrast procedure, revealed Gaucher cells in the spleen, liver, lungs, lymph nodes, bone marrow, thymus and adrenal glands. Nonspecific degenerative changes were also observed in the cerebral cortex. Chemical examination of the spleen revealed kerasin with sugar components of D-glucose.

FROM THE AUTHORS' SUMMARY.

IODOMETRIC DETERMINATION OF CHLORIDES IN THE BLOOD. J. STYBLO, Pediat. listy **3**:202, 1948.

The author describes the technic and his good results with the use of the modified Sendrei method.

FROM THE AUTHOR'S SUMMARY.

LEUKEMIA IN CHILDREN. J. M. TORORELLA O. and R. SOTO A., Pediat. Américas **6**:180 (March) 1948.

From 1943 to 1946 20 children with leukemia were admitted to the Hospital Infantil, México, D. F., Mexico. These constituted 0.05 per cent of all patients admitted during that period. The authors discuss the disease in these patients, pointing out the usual symptomatology and blood findings. Eighty-five per cent had acute leukemias, 80 per cent being lymphocytic and 5 per cent myelocytic.

DE LA TORRE, México, D. F., Mexico.

PROTHROMBIN LEVELS IN THE MATERNAL BLOOD AT THE END OF PREGNANCY AND IN THE CORD BLOOD. J. BALES, P. IZARN and NICOUL, Pédiatrie **36**:492 (Nov.-Dec.) 1947.

The authors set out to study the probability of increased prothrombin levels in maternal blood (postpartum thrombosis) or decreased levels (hemorrhagic tendency of the infant) and the level of prothrombin of the cord blood at birth and its relation to the level in the mother's blood. The Quick method of prothrombin determination was used on 40 pregnant women. Thirty were noted to have normal or near normal prothrombin levels; 5 mothers each had either hypoprothrombinemia or hyperprothrombinemia, but none under 50 or above 150 per cent. The cord blood of 26 infants varied in 23 between 30 and 60 per cent of normal and the level in 3 was 75 per cent, with an average of 47 per cent of normal. Since according to the authors' experience the cord blood equals the infant's blood, infants have hypoprothrombinemia of about 50 per cent as compared with maternal blood. Furthermore, if the blood was conserved with potassium oxalate for forty-eight hours, the prothrombin of the cord blood disappeared much faster than that of the maternal blood, indicating a difference in quality as well. Since the relation between prothrombin levels in maternal and cord blood appeared to be constant (40 to 50 per cent), the administration of vitamin K to the pregnant woman seems indicated.

GLASER, Chicago.

CARDIAC ARRHYTHMIA IN AN INFANT WITH MULTIPLE DEFICIENCY SYNDROME. R. SCHIFFRIN and E. SEPULVEDA, Rev. chilena de pediat. **19**:455 (June) 1948.

A case of nutritional edema with cardiac symptoms in a 14 month old infant hospitalized in the Manuel Arriaran Hospital, Santiago, Chile, is reported. Clinical and phonocardiographic examination revealed an arrhythmia, with partial progressive auriculoventricular heart block seen on the electrocardiographic studies. The arrhythmia disappeared with the improvement of his general condition and with administration of phenobarbital and atropine. A review of the literature with special reference to auriculoventricular heart block in infants is presented.

FROM THE AUTHORS' SUMMARY.

GLYCOGENOLYTIC ACTION OF THE BLOOD IN NORMAL CHILDREN AND IN THOSE WITH SOME CHILDHOOD DISEASES. ANGELO CHIEFFI and ANSELMO CALAMARI, Riv. clin. pediat. **45**:641 (Nov.) 1947.

In this first of two articles the authors report the results of studies on the glycogenolytic power of the blood in normal children and in others affected by various diseases. They suggest the importance of the use of the modified method of Ottenstein for this purpose. A deficit of glycogenolytic enzymes was observed in infants a few months old, especially in premature infants and in those with pathologic changes resulting from some diseases, particularly epidemic parotitis and diseases in which the liver is seriously affected.

FROM THE AUTHORS' SUMMARY.

PLACE OF CHLOROMA AMONG DISEASES OF THE BLOOD. R. GIUNTINI, Riv. clin. pediat. **46**:108 (Feb.) 1948.

A case of chloroma with typical cranio-ophthalmic localization and with a remarkable accumulation of fluid in the peritoneal cavity is described. In the sediment of this fluid elements similar to hemocytoblasts prevailed but the cells were not according to type as regards structure, shape and dimension.

In observing this case, the author had the opportunity to study the problem of the nosologic position of chloroma in the total picture of the hemopathies in the light of the most recent observations on pathologic states of the blood. From these considerations, the conclusion is drawn that for chloroma, as for leukemia, the basic pathogenetic element is an anaplastic-aplastic process of the hemopoietic centers, the characteristics of which blend into those of the neoplastic process. Therefore, in his opinion, the chloroma is a special clinical form of acute leukemia of a predominantly hemocytoblastic type, and leukemia, in turn, is an unusual neoplasm of the hemolymphopoietic tissues.

FROM THE AUTHOR'S SUMMARY.

FAILURES OF SPLENECTOMY IN THROMBOPENIC PURPURA (WERLHOF'S DISEASE). UBALDO PELLEGRINI, Riv. clin. pediat. **46**:120 (Feb.) 1948.

The author, after a review of the medical literature on the results of removal of the spleen in thrombopenic purpura (Werlhof's disease), reports the case of a 9 year old girl with a constitutional type of the disease. She died from purpura of the brain eleven months after splenectomy. The author is of the view that the latest pathogenetic opinions on this disease, which consider it as an alteration of the entire reticuloendothelial system, can well explain the failure of splenectomy in this case.

FROM THE AUTHOR'S SUMMARY.

EARLY OPERATION IN CONGENITAL DISEASES OF THE HEART AND GREAT BLOOD VESSELS. I. BOERRMA, Bull. schweiz. Akad. d. med. Wissensch. **4**:66 (July) 1948.

A report is given on several cases of congenital heart disease (arterial aneurysm, pulmonary stenosis, arteriovenous fistula) in which operation was performed with success and which presented difficulties in diagnosis or in the indications for operation.

FROM THE AUTHOR'S SUMMARY.

A SIMPLE GRAPHIC METHOD FOR DETERMINATION OF COLOR INDEX. G. BUGYI, Paediat. danub. **4**:153 (Sept.) 1948.

While all biologic values are usually recorded in absolute quantities, the use of Sahli values for the hemoglobin content of the blood is still current. It is commonly accepted that a hemoglobin content of 16 Gm. per hundred cubic centimeters corresponds to the normal value. This quantity should, therefore, be taken for 100 per cent. Thus,

$$\text{Color index} = \frac{100 \times \text{Hb value}}{2\ \text{RBC}} = \frac{K \times \text{Hb per cent}}{2\ \text{RBC}}$$

According to our calculations, K is equal to 6.25.

A table consisting of three parallel vertical lines was constructed. On the two far lines figures for red blood cells and various hemoglobin contents expressed in grams per hundred cubic centimeters, and on the middle line the color indexes, were placed. By connecting the point corresponding to a certain number of red blood cells with the hemoglobin value by a straight line, the color index can be read on the middle line at the point of intersection. Thus, the color index can easily be reckoned without the determination of the absolute quantity of hemoglobin, and the use of two parallel scales of hemoglobin values is rendered superfluous.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

MAURIAC'S SYNDROME (GLYCOGENOSIS AND HEPATOMEGALY). A. HANNS, Presse méd. **56**:339 (May 8) 1948.

The author presented the case of a boy of 14 in whom intractable diabetes had developed at the age of 6. His liver was large and his spleen normal. His growth had stopped; sexual development had not begun. He had deposits of fat on the trunk and face. His intelligence and disposition were normal, but he was incapable of any muscular exertion.

Various forms of glycogenosis were discussed. DAFFINEE, Melrose, Mass.

ATRESIA AND STENOSIS OF THE ESOPHAGUS CAUSED BY A CONGENITAL MEMBRANOUS DIAPHRAGM. GUILLEMINET and LACOUR, Pédiatrie **36**:197 (May-June) 1947.

Most congenital malformations of the esophagus are instances of atresia with tracheoesophageal fistula which until recently were inaccessible to treatment. Guilleminet and Lacour are concerned with a much rarer condition, a diaphragm which partially or totally obstructs the esophagus and which can be treated endoscopically.

A newborn girl vomited all the food given to her. Roentgen study with barium sulfate revealed complete obstruction of the esophagus. A catheter, inserted

through the esophagoscope, did not penetrate, but a harder tube overcame the resistance and food entered the stomach through this tube. The child then received dilation treatments, but after three years she again showed signs of esophageal obstruction. At that time the esophageal wall was cut outside the mucosa, and from then on the child had no difficulties in swallowing.

The authors found only 14 cases reported in the literature. In each the malformation consisted of either stenosis or atresia by a diaphragm, the former occurred more frequently. The lesion is congenital, coexists frequently with other malformations and is usually found in the lowest third of the esophagus above the cardia. Nothing is known of the origin of the malformation, but germ damage is suggested. As diagnostic procedures, catheterization is less satisfactory than roentgen examination with a roentgenopaque bougie; still better is esophagoscopy, which permits the study of the character of the esophageal wall and the location of the membrane and a possible opening. The authors insist on prolonged dilation of the esophagus; others suggest circular electrocauterization. Sometimes operation may be necessary, as in the case reported.

GLASER, Chicago.

ON SOME TROPICAL ASPECTS OF LIVER PATHOLOGY IN PEDIATRICS. EUGENE STRANSKY and DOMICIANA F. DAUIS-LAWAS, Ann. pædiat. **170**:131, 1948.

A case of amebic abscess in a child 7 years of age is presented with the autopsy report. Besides a solitary large hepatic abscess, there was severe intestinal hemorrhage from an amebic ulcer in the colon. The hepatic abscess ruptured into the peritoneal cavity, causing diffuse peritonitis. The amebic infection was silent.

A case of a hepatic abscess, which also ruptured into the peritoneal cavity, secondary to migration of ascarides into the common bile duct and from there into the hepatic duct and its tributaries, is presented. The literature on hepatic abscesses of both amebic and Ascaris causation is shortly discussed.

Three cases of malignant new growth of the liver are presented. The first was a case of primary carcinoma of the liver in a 9 year old girl, diagnosed by the results on aspiration biopsy. The second was a probable case of primary sarcoma of the liver in a 17 month old female infant, also diagnosed by the results on aspiration biopsy, and the third was a probable case of primary malignant tumor of the spleen with metastases in the liver and bone marrow in a 3 year old male child.

The peculiarities of infectious hepatitis in the tropics are shortly discussed. A case is presented of severe anemia suggesting chronic familial hemolytic anemia, which proved to be infectious hepatitis with long-standing ancylostomiasis. Another case was reported of severe anemia in an infant 2 months of age in which the anemia was considered a consequence of hepatitis. It is stressed that anemia in the first years of life is much more widespread in the tropics than in the temperate climates. Therefore, anemia accompanying or complicating hepatitis is much more frequent in the tropics than elsewhere.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF PNEUMOCOCCIC PERITONITIS WITH PENICILLIN. VLADIMIR MAZAL, Ann. pædiat. **170**:252 (May) 1948.

In a review of 111 cases of Pneumococcic peritonitis, the various views and tendencies in the treatment of this disease during the last seventeen years are cited. The author's experience with 21 patients treated with penicillin is thoroughly discussed. In all patients, laparotomy and appendectomy were performed and 50,000 to 100,000 Oxford units of penicillin was deposited in the abdominal cavity. After the operation, 10,000 to 15,000 units of penicillin was administered

every three hours intramuscularly, until the pathologic symptoms disappeared. Based on this experience, the author strongly recommends laparotomy and appendectomy with administration of penicillin, both intra-abdominally and intramuscularly, as the method of choice in treatment and diagnosis of pneumococcic peritonitis.

FROM THE AUTHOR'S SUMMARY.

DIAGNOSIS AND PRESENT TREATMENT OF PNEUMOCOCCIC PERITONITIS. G. TÖRÖK, Ann. paediat. **170**:263 (May) 1948.

In the early stages of pneumococcic peritonitis the erythrocyte sedimentation rate is a valuable diagnostic help. It should be used even when there is no pronounced leukocytosis. It is significant that the sedimentation rate is higher than in acute appendicitis. Sulfonamide therapy cannot prevent abscess formation in spite of improvement of symptoms. It should be given up in patients with leukopenia and in those whose blood shows no shift to the left.

Treatment with penicillin is preferable. If applied early it will prevent abscess formation. After abscess formation it makes major surgical intervention unnecessary. If the abscess can be approached from the outside without difficulty or if there is an umbilical fistula, the discharge will stop with penicillin treatment even when it has been going on for months.

FROM THE AUTHOR'S SUMMARY.

RESORPTION OF BLOOD AFTER INTRA-ABDOMINAL BLEEDING. BO VAHLQUIST, Helvet. paediat. acta **3**:17 (Feb.) 1948.

Massive hemorrhage into the abdominal cavity, probably due to hepatic damage, gave rise to severe anemia in a 7 day old boy. After a single blood transfusion (45 cc. intravenously) the blood values of the child rose in eight days from 6.1 Gm. of hemoglobin per hundred cubic centimeters and 2,100,000 erythrocytes to 15.6 Gm. and 4,000,000 cells, respectively. It is reasonable to assume that the amazingly rapid increase was due mainly to resorption of the blood from the abdominal cavity. The time interval observed between the bleeding and the restoration of the blood values is in good correspondence with the results obtained in experiments with tagged erythrocytes.

FROM THE AUTHOR'S SUMMARY.

VOMITING AND ESOPHAGEAL MALFORMATIONS IN THE INFANT. A. VOGT, Helvet. paediat. acta **3**:46 (Feb.) 1948.

A case of brachyesophagus was followed for one year. The infant, at the age of 4 to 5 months, presented blood-tinged vomitus, which increased when the child was recumbent and which recurred with a certain periodicity. The weight of this child was clearly under normal. The roentgenographic examination revealed shortness of the esophagus and an ectopic stomach. The prognosis was better after the first year of life, when the infant was able to masticate his food. Treatment is aimed chiefly at carrying him through the first years of infancy.

FROM THE AUTHOR'S SUMMARY.

CEPHALIN CHOLESTEROL FLOCCULATION TEST. J. A. LOTERIJMAN, Nederl. tijdschr. v. geneesk. **92**:1696 (June 5) 1948.

The cephalin cholesterol flocculation test of Hanger is a reliable and simple means of determining damage to the hepatic parenchyma. The reaction is positive when cirrhosis or inflammation of the liver is present, as well as when the liver is secondarily affected as in chronic infections and in some acute infectious diseases,

such as diphtheria and typhoid. If a positive reaction in infectious hepatitis, congenital syphilis and malaria soon becomes negative, the prognosis is favorable; if it remains positive for several months, the hepatic structure is severely damaged. To obtain reliable results, one must use a stabilized reagent.

The results of the cephalin cholesterol flocculation test do not parallel those of the Takata-Ara and formol-gel tests. No correlation was found between the result of this test and the content of protein fractions in the serums.

In this investigation positive results were obtained in patients with infectious hepatitis, cirrhotic hepatitis, congenital syphilis, measles and malaria. In some cases of chronic infections, such as pyelitis and pericarditis, the reactions proved to be positive. In the serums of 23 healthy children serving as a control group no flocculation was seen.

VAN CREVELD, Amsterdam, Netherlands.

CONGENITAL ESOPHAGEAL ATRESIA WITH AN ESOPHAGOTRACHEAL FISTULA. T. COUFALÍK, Pediat. listy **3**:29 (Jan.) 1948.

An atresia of the upper and middle thirds of the esophagus is described in a 3 day old full term baby, who died on the fourth day. The clinical symptoms, pathogenesis and diagnosis are discussed.

FROM THE AUTHOR'S SUMMARY.

SUBMUCOUS ENTEROCYSTOMA OF THE CECUM AND THE LOSSER-DEBRAY-MILKMAN SYNDROME. J. VÝBORNÝ, Pediat. listy **3**:31 (Jan.) 1948.

The author describes a case of a submucous enterocystoma of the cecum combined with the picture of a symmetric linear reconstruction of the bones on both tibias (Losser-Debray-Milkman syndrome) in a boy 5 years of age. The enterocystoma caused a huge invagination. Surgical disinvagination, enterotomy, resection of the tumor and suture of the colon were done. He died twenty-eight hours after the operation. A summary of the pathogenesis is given; the clinical course and the therapeutic possibilities of both rare diseases are discussed in the light of the current literature. Another author has, nevertheless, suggested a causal connection between the diseases. The enterocystoma was probably the only evident manifestation of the large defect of the gastrointestinal tract, which caused a metabolic disturbance, manifested in the bones by the osteopathy.

FROM THE AUTHOR'S SUMMARY.

ACUTE REGIONAL ILEITIS. H. J. NOTTI and J. J. GIUNTA, Arch. argent. de pediat. **29**:109 (March) 1948.

The patient presented the clinical picture of acute appendicitis. He was operated on and observed to have a normal appendix. The affected portion of the ileum was not resected. Spontaneous recovery followed the laparotomy. The patient has been well for three years after the operation, without thus far presenting symptoms of chronic ileitis.

ROJAS, Boston.

TWO CASES OF MALIGNANT TUMOR OF THE STOMACH IN YOUNG PATIENTS. T. MEUWISSEN, Maandschr. v. kindergeneesk. **16**:402, 1948.

These 2 cases are characteristic in that, although the diagnosis was made in due time, the tumor was inoperable.

The first patient, a youth, 19 years of age, complained of stomachache shortly after dinner and had suffered from anorexia for seven months. Other than hypersensibility in the epigastrium, no clinical symptoms were found. The hydrochloric

acid in the stomach was normal. The roentgenogram of the stomach showed a lacunar image and other signs of malignancy. The tumor was found to be inoperable.

The second patient, a girl 14 years old, for several months had diffuse pains in the abdomen and anorexia. She tired very easily and had lost weight. Clinical examination revealed beginning emaciation and a slight muscular defense in the epigastrium. A benzidine test of the gastric content gave a positive reaction. The roentgenogram revealed the existence of a malignant tumor, which proved to be inoperable. Anatomically, the previous diagnosis was confirmed for this patient.

VAN CREVELD, Amsterdam, Netherlands.

VITAMIN K IN TREATMENT OF CIRRHOSIS OF THE LIVER. MÜFIDE KÜLEY, Schweiz. med. Wchnschr. **79**:365 (April 23) 1949.

Several patients with more or less certain cirrhosis of the liver were treated with a vitamin K preparation. It is recommended that this therapy be used even in severe cases.

AMBERG, Rochester, Minn.

PERISTALTIC ACTIVITY OF ANIMAL BILE. H. BRÜCKE, Wien. klin. Wchnschr. **61**:241 (April 22) 1949.

Fresh bile of cattle given as a drop enema in cases of persistent constipation proved effective for a period often lasting several days to two weeks. A good result was obtained in cases of intestinal paralysis with or without peritonitis when bile was given by duodenal tubes.

AMBERG, Rochester, Minn.

PROBLEMS OF OPERATIVE INDICATION IN PNEUMOCOCCAL PERITONITIS. K. FRANK, Paediat. danub. **4**:117 (Sept.) 1948.

From the points of view of prognosis and surgical therapy alike, the clinical picture of pneumococcic peritonitis has changed much since the introduction of modern antibiotic and chemotherapeutic drugs. It may be inferred from the observations made on 50 patients of the pediatric department of the University of Pécs, Hungary, that the crucial problem is early diagnosis rather than management.

The following points arise when a patient suspected of pneumococcic peritonitis is admitted to the hospital: 1. An accurate history should be taken regarding the onset of the process. 2. Blood counts and sedimentation rates should be determined; the bacterial flora of the vagina and the peritoneal exudate should be examined. 3. In positive cases, those patients ill not longer than three days should be treated with antibiotics (penicillin and sulfathiazole). 4. If more than five days have elapsed, laparotomy should be performed to remove the gross fibrin masses and pus. The abdomen may be closed after penicillin has been placed in the lesion. The internal management described previously should be commenced. 5. Encapsulated abscesses should be opened and drained. 6. In acute cases, characterized by equivocal symptoms and negative bacteriologic findings in the vaginal and abdominal secretions, exploratory laparotomy is advisable.

FROM THE AUTHOR'S SUMMARY.

GLYCOGENOSIS ASSOCIATED WITH DIABETES MELLITUS. L. BARTA and J. LÁSZLÓ. Paediat. danub. **4**:127 (Sept.) 1948.

In a girl 4 years of age symptoms of glycogenosis were associated with those of diabetes mellitus. The prominent clinical features were a high blood sugar

level, insulin sensitivity, lack of ketonuria and an enormous enlargement of the liver. The steep and protracted curves following administration of dextrose, galactose and levulose and the missing Staub-Traugott effect after a double dextrose tolerance test pointed to an alteration of the carbohydrate metabolism. To doses of epinephrine and anterior pituitary the patient reacted with an increase in the blood sugar level amounting to about 100 per cent of the fasting level. Following administration of adrenal cortex extracts, the blood sugar curve became flat and the Staub-Traugott effect returned.

Histologic examination revealed the classic evidences of glycogenosis (von Gierke's disease). Severe destruction of the basophil elements and colloid retention and proliferation of the connective tissue were found in the anterior lobe of the pituitary. This observation supports the presumption that in glycogenosis a prominent part is played by the pituitary-diencephalon system. The peculiar hormonal conditions prevailing in childhood may constitute a predisposition to severe disturbances of glycogen metabolism, though mild disorders may occur also in adults in connection with pituitary diseases.

The disturbance of fermentative decomposition may also bear a relation to neurohormonal dysfunctions. The autonomous nervous system, being closely related to hormonal functions, may stimulate or inhibit hepatic function. The contrast between the dextrose and galactose balance is not invariably due to congenital anomalies of the enzyme system of the liver but may arise also in consequence of hormonal dysfunctions.

The results of the examinations suggested that the characteristic symptoms of glycogenosis depend on extension of the damage to the pituitary-diencephalon system. By this approach the great variety of the consecutive symptoms, such as nanosomia, the presence or absence of acetonuria, osteoporosis, pigmentations and the disorders of the water and salt metabolism, may readily be understood.

FROM THE AUTHORS' SUMMARY.

CONGENITAL ATRESIA OF THE BILE DUCTS. SHOU-HO CHU, YEN-HUA SUN, CH'I-HUA TSO, and CHEIN-HUNG CHEN, Chinese M. J. **66**:609 (Nov.) 1948.

Gradually increasing jaundice was first noticed in a male infant at the age of 1 month. An operation at the age of 5 months revealed biliary cirrhosis of the liver and complete absence of the extrahepatic ducts. The patient died on the tenth postoperative day.

MACDONALD, Pittsburgh.

Nervous Diseases

CRANIOSTENOSIS: FAILURE OF MYELINATION; ANOMALIES OF CEREBRAL CORTEX AND CEREBELLAR HYPOPLASIA. CORNELIA DE LANGE, Ann. pædiat. **171**:65 (Aug.) 1948.

A newborn child with microcephaly had frequent and violent attacks of convulsions. The child died on the fourth day of life. There proved to be craniostenosis, anomalies of the cerebral cortex, cerebellar hypoplasia and a total lack of myelination. The author stresses the fact that malformation of the brain may be a cause not only of convulsions in the neonatal period but possibly also of those occurring after a silent period of some months.

FROM THE AUTHOR'S SUMMARY.

SPASTIC PARALYSES OF THE RIGHT ARM AND FAMILIAL LEFTHANDEDNESS. G. FANCONI, Helvet. paediat. acta **3**:64 (Feb.) 1948.

The patient displayed spastic paralysis of the right arm. There was an accumulation of lefthanded males in the father's family. The mother stuttered. It is supposed that the hemiparesis of the baby is the result of the combined effect of the genes that were connected with a deficiency of the left hemisphere.

FROM THE AUTHOR'S SUMMARY.

COMPRESSION OF SPINAL CORD BY AN ANGIOMA. V. POTUCEK, Pediat. listy **3**:25 (Jan.) 1948.

The author describes the case of an 8½ year old girl in whom an acute, asymmetric, slowly progressing paresis of the lower extremities developed which led, after approximately six months to an almost complete paraplegia of the lower extremities. At the same time a beginning defect of the sensory innervation commenced. There was no defect in the sphincters. Roentgenologic examination of the spine revealed on the corpus, arch and transverse process of the fifth dorsal vertebra signs indicating an angioma. This finding was confirmed by operative and histologic examination. A hemangioma in the spinal canal the size of a cherry was removed. Neurologic symptoms disappeared within a month.

FROM THE AUTHOR'S SUMMARY.

STREPTOMYCIN TREATMENT IN INFLUENZAL MENINGITIS. J. MICHALICKOVA, J. GRUJBAR and D. BLASKOVIC, Pediat. listy **3**:185, 1948.

The authors report 2 cases of meningitis caused by Hemophilus influenzae in children, aged 14 and 15 months. H. influenzae, type B, was observed in 1 case. In the 2 cases cure was brought about by streptomycin treatment, following the unsuccessful use of sulfonamides and penicillin.

FROM THE AUTHORS' SUMMARY.

STURGE-WEBER'S DISEASE. OLE BENTZEN, Nord. med. (Hospitalstid.) **33**:465 (Feb. 21) 1947.

Report of successful operations on 2 patients with Sturge-Weber disease is given. One of the patients was a girl of 5 years; the other, an adolescent girl of 17. The former had since birth had a large hemangioma on the left side of the face. Nine months before admission she had suffered a trauma to her head, with unconsciousness for one hour. During the last three months she had displayed convulsions of the right side, without unconsciousness. There were calcifications in the left occipital sulcus. Encephalography revealed no abnormal condition, but the electroencephalogram was difficult to interpret. Craniotomy with lobectomy of the occipital lesions of the left side was performed. After the operation she was free from seizures during six months of observation. The second patient had suffered from epileptic fits since infancy; she had a hemangioma on the left side of the face and was somewhat feebleminded. She displayed right-sided homonymous hemianopsia and calcifications in the left occipital sulcus. A craniotomy with extirpation of the intracranial hemangioma was performed. After the operation the patient was free from convulsions during an observation time of six months.

WALLGREN, Stockholm, Sweden.

Diseases of the Genitourinary Tract

URINARY LYSOZYME: III. LYSOZYMURIA IN CHILDREN WITH THE NEPHROTIC SYNDROME. ARMINE T. WILSON and WILLIAM P. HADLEY, J. Pediat. **36**:199 (Feb.) 1950.

Wilson and Hadley have reported previously that healthy children and children with miscellaneous diseases rarely excrete more than 32 units of lysozyme per milliliter of urine. In this study, 10 of 14 children with the nephrotic syndrome showed increased urinary lysozyme. No uniform patterns of lysozyme excretion were found, but, in general, borderline or increased lysozyme excretion was found in those patients with reduced urea clearance, nitrogen retention and reduced ability to concentrate urine. Normal lysozyme values were found in those patients with elevated urea clearance, normal plasma urea nitrogen and normal ability to concentrate urine. The degree of lysozymuria was not related to the severity of proteinuria or hypoproteinemia.

MACDONALD, Pittsburgh.

ELECTROENCEPHALOGRAPHIC FINDINGS IN ACUTE NEPHRITIS. JAMES G. HUGHES, FONTAINE S. HILL and BILLIE DAVIS, J. Pediat. **36**:451 (April) 1950.

Repeat electroencephalograms were obtained for 24 patients with acute nephritis. Twenty-two of these patients showed electroencephalographic abnormalities. The chief changes were bursts of slow frequency waves of high microvoltage, instability of the electroencephalographic pattern and suppression of the alpha activity associated with an increase of fast frequencies of low amplitude. The abnormalities increased day after day as the nephritis persisted, and potentials returned toward normal as the nephritis receded. All of 12 patients with nervous system symptoms showed abnormal brain potentials. The authors believe that the electroencephalogram is a more sensitive approach to the determination of cortical dysfunction in this disease than are previous methods. They could not demonstrate a correlation between the electroencephalogram and the degree of hypertension or the clinical condition of their patients.

MACDONALD, Pittsburgh.

NEPHROTIC SYNDROME: I. NATURAL HISTORY OF THE DISEASE. LEWIS A. BARNESS, GRETCHEN H. MOLL and CHARLES A. JANEWAY, Pediatrics **5**: 486 (March) 1950.

The records of 208 patients with the nephrotic syndrome seen from 1926 to 1948 have been reviewed. The main criteria found for differentiating between lipid nephrosis and the nephrotic stage of chronic glomerulonephritis have been the presence of hypertension and azotemia for longer than one month in patients with the latter disease.

Lipid nephrosis is characterized by the insidious onset of edema in young children, usually between the ages of 1 and 4 years. Significant signs include edema, hypoproteinemia, hypercholesteremia and heavy proteinuria. Symptoms and signs in lipid nephrosis usually persist from one to three years without specific therapy. The prognosis is not related to the number of remissions and exacerbations and has improved with the advent of sulfadiazine and the newer antibiotics, since infection is responsible for most deaths.

In the nephrotic stage of chronic glomerulonephritis, on the other hand, the prognosis is still poor and renal failure is the major cause of death.

Diseases of Ductless Glands; Endocrinology

THE RELATION OF THYROXINE TO TOTAL IODINE IN THE THYROID GLAND. A. WOLFF and I. L. CHAIKOFF, Endocrinology **41**:295 (Oct.) 1947.

The work of many investigators has made it clear that 90 per cent or more of the iodine in the normal thyroid gland is present in organic combination. This organic iodine, according to Harington, can be completely accounted for by thyroxine and diiodotyrosine. These two compounds are not normally free in the gland but can be isolated after suitable hydrolysis of the thyroid protein. In this paper the results of the study of eleven different species of vertebrates are recorded. The ratio of thyroxine iodine to total iodine remains relatively constant from species to species and from animal to animal within a given species.

JACOBSEN, Buffalo.

EFFECTS OF STEROIDS ON LACTATION. J. C. BARSANTINI and GEORGES M. C. MASSON, Endocrinology **41**:299 (Oct.) 1947.

The inhibitory effect on lactation of all steroids examined is entirely mediated through the ovaries, since these steroids are inactive in spayed lactating animals. There appears to be some relation between the luteotrophic effect of steroids and their ability to inhibit lactation.

JACOBSEN, Buffalo.

THE SIGNIFICANCE OF THE ENDOCRINE GLANDS IN THE RIPENING OF RETICULOCYTES. BORGE GOTFRED CHRISTENSEN and CLAUS MUNK PLUM, Endocrinology **41**:347 (Nov.) 1947.

Anemia combined with a decreased number of erythrocytes was observed in most of the rats in this study after hypophysectomy. Reticulocytes were increased after hypophysectomy and after thyroidectomy.

It is concluded that the thyroid gland produces substances which are of importance to the activation of the ripening substances in the organism and that this function is controlled by the hypophysis.

JACOBSEN, Buffalo.

EFFECTS OF LOW BAROMETRIC PRESSURE ON THE CHEMICAL COMPOSITION OF THE ADRENAL GLANDS AND BLOOD OF RATS. JAY TEPPERMAN, HELEN M. TEPPERMAN, BARABA W. PATTON and LESLIE F. NIMS, Endocrinology **41**:356 (Nov.) 1947.

The cholesterol ester content of the adrenal glands of rats exposed to varying degrees of anoxia for five hours was found to diminish in a curvilinear fashion with increase in altitude up to 25,000 feet (7,620 meters). The mean control value at sea level was 5.48 per cent, whereas the value at 25,000 feet was 2.46 per cent. At 28,000 feet (8,534 meters), however, the determined point failed to conform with the previously ascertained curve. At a simulated altitude of 20,000 feet (6,096 meters) striking hyperventilation and pronounced hyperreflexia were observed in conjunction with an appreciable fall in adrenal cholesterol ester, while studies of other blood constituents revealed only minor deviations from the normal values. Future understanding of the mechanism whereby the prevention of

acapnia alters the response of the adrenal glands to anoxia will yield basic information concerning the function of these glands.

JACOBSEN, Buffalo.

HORMONAL FACTORS RESPONSIBLE FOR DEPOSITION OF CHOLESTEROL IN THE CORPUS LUTEUM OF THE RAT. JOHN W. EVERETT, Endocrinology **41**:364 (Nov.) 1947.

A rich deposition of cholesterol occurred in the corpora lutea of the pregnant rat forty-eight hours after injection of estradiol benzoate U. S. P. (2 micrograms or more) or after implantation of small estradiol crystals. Slight accumulation was in progress twenty-four hours after estrogen administration, but the major change coincided, approximately, with induced ovulation (circa thirty-six hours). The presence of the hypophysis was essential. The observations add to the body of evidence which indicates that cholesterol is a precursor of progesterone.

JACOBSEN, Buffalo.

SEX AND DIABETES. V. G. FOGLIA, N. SCHUSTER and R. R. RODRIGUEZ, Endocrinology **41**:428 (Nov.) 1947.

A study on rats with 95 per cent pancreatectomy showed that diabetes is more frequent and appears earlier in males than in females. The sexual difference seems to be related to the protective action of feminine hormones.

JACOBSEN, Buffalo.

THE ANTITHYROID EFFECT OF CERTAIN FOODS IN MAN AS DETERMINED WITH RADIOACTIVE IODINE. MONTE A. GREER and E. B. ASTWOOD, Endocrinology **43**:105 (Aug.) 1948.

Although iodine deficiency is well established as an etiologic factor in endemic goiter, it sometimes appears that other agents may be responsible. A variety of foods has been shown to have goitrogenic activity. Recently, the determination of antithyroid activity by observation of the inhibition of the radioactive iodine uptake was noted to provide a rapid and convenient method for assay of the effect of various foods in man. Using this method, the authors report that the antithyroid effect of sixty-one different foods was tested in 100 different subjects with radioactive iodine. Of these, rutabaga was found to possess the greatest antithyroid activity. Vegetables were more active than animal products.

JACOBSEN, Buffalo.

HISTOLOGICAL EFFECT OF THIOURACIL ON THE FETAL THYROID OF THE MOUSE. G. KAUFFMAN, V. HURST and C. W. TURNER, Endocrinology **43**:187 (Sept.) 1948.

The purpose of this work was to ascertain the time at which the fetal thyroid of the mouse begins secretory activity and to determine the effect of thiouracil on the growth and development of the fetal thyroid. Evidence is presented which indicates that in the mouse thyroid follicle and colloid formation begins on the sixteenth day of fetal life. Feeding 0.2 per cent thiouracil to the mother was observed to inhibit the formation of thyroid follicles and to depress colloid formation in the fetus. It is the authors' opinion that this effect is due to the passage of thiouracil through the placenta.

JACOBSEN, Buffalo.

EFFECTS OF PITUITARY ADRENOCORTICOTROPHIC HORMONE ON THE INTACT RAT, WITH SPECIAL REFERENCE TO CYTO-CHEMICAL CHANGES IN THE ADRENAL CORTEX. GRACE E. BERGNER and HELEN WENDLER DEANE, Endocrinology **43**:240 (Oct.) 1948.

The results of experiments here reported are interpreted as indicating that adrenocorticotropin causes an increased secretion of 11-oxygenated ("sugar") hormones by the zona fasciculata of the rat but fails to increase the secretion of the salt-retaining hormones by the zona glomerulosa.

These results have been compared with those in man. Contrary to the observations on the rat, both types of hormone appear to be released in man following the administration of adrenocorticotropin, a result suggesting a species difference.

JACOBSEN, Buffalo.

THE CORRELATION OF THE CIRCULATING POLYMORPHONUCLEAR LEUCOCYTES (NEUTROPHILES) WITH THE ADRENAL ASCORBIC ACID IN THE RAT. ABRAHAM DURY, Endocrinology **43**:336 (Nov.) 1948.

This paper presents evidence of the statistically significant correlation of the adrenal ascorbic acid with the polymorphonuclear leukocytes and the alternation of this relationship with administration of certain drugs.

JACOBSEN, Buffalo.

FURTHER STUDIES ON THE PROTECTIVE POWER OF ADRENAL EXTRACT AND STEROIDS AGAINST TOXIC AGENTS. LENA A. LEWIS and IRVINE H. PAGE, Endocrinology **43**:415 (Dec.) 1948.

Adrenalectomized rats succumbed more quickly to bacterial toxins than normal rats. A protective power of adrenal hormones against the action of bacterial toxin, whether endotoxin such as typhoid or exotoxin as botulinus or a combination as diphtheria toxin, seems to parallel its action on carbohydrate rather than on electrolyte metabolism. For example, in the protection given adrenalectomized rats against botulinus toxin by adrenal extract, the gluconeogenic action of the hormone probably plays an important part.

JACOBSEN, Buffalo.

GROWTH INHIBITION IN BONE AND BONE MARROW FOLLOWING TREATMENT WITH ADRENOCORTICOTROPIN. BURTON L. BAKER and DWIGHT J. INGLE, Endocrinology **43**:422 (Dec.) 1948.

The following changes were observed in the tibias of adult male rats treated with adrenocorticotropic hormone in doses of 1 and 3 mg. daily for twenty-one days: (1) retardation of chondrogenesis and osteogenesis and (2) atrophy of the red marrow, with apparent replacement of it with fat.

The retardation of chondrogenesis and osteogenesis assumes its greatest significance when viewed in the light of the growth-inhibiting potentiality of the adrenocorticotropic hormone. Apparently, these end effects are elicited through the stimulated release by the adrenal cortex of the 11-oxysteroids.

JACOBSEN, Buffalo.

THE DIFFERENTIAL MECHANISMS BY WHICH PICROTOXIN AND COPPER ACETATE INDUCE OVULATION IN THE RABBIT. CHARLES H. SAWYER and J. E. MARKEE. Endocrinology **46**:177 (Feb.) 1950.

A study of the mechanisms by which picrotoxin and copper salts induce ovulation in the rabbit presents evidence that, whereas picrotoxin definitely functions by way of the nervous system, at least a large part of the copper stimulus is exerted directly on hypophysial cells.

Picrotoxin-induced ovulation was always preceded by convulsions; in their absence pituitary activation failed to occur.

Ovulation was induced by copper acetate in a dosage which produced no overt signs of nervous stimulation. The copper stimulus to ovulation was not blocked by the antiadrenergic, the anticholinergic or the anticonvulsive agent. Finally, pituitary activation was achieved by injecting tiny amounts of copper acetate directly into the adenohypophysis.

Preliminary treatment with estrogen facilitates both neurogenically induced and copper-induced ovulation. It is suggested that the steroid acts at the hypophysial level by lowering thresholds to both neurohumoral and direct chemical stimulation.

JACOBSEN, Buffalo.

THE EXCRETION OF POSTERIOR PITUITARY ANTIDIURETIC HORMONE IN THE URINE AND ITS DETECTION IN THE BLOOD. ROSE G. AMES, DAN H. MOORE and H. B. VAN DYKE, Endocrinology **46**:215 (Feb.) 1950.

It has been clearly demonstrated in rats that an effective osmotic stimulus, such as dehydration or the administration of hypertonic saline solution, could cause the secretion of posterior pituitary antidiuretic hormone, which was detected after its excretion in the urine.

The form in which antidiuretic hormone is secreted by the posterior lobe of the pituitary gland and in part excreted subsequently by the kidneys is unknown.

The experiments reported are in harmony with the view that antidiuretic hormone is excreted in the urine of the dog as a large molecule, as shown by its sedimentation in the ultracentrifuge.

JACOBSEN, Buffalo.

RESUMPTION OF FUNCTION OF AUTOPLASTIC ADRENOCORTICAL TRANSPLANTS TO THE DORSAL MUSCULATURE IN RATS. EUGENE L. KOMRAD and LELAND C. WYMAN, Endocrinology **46**:228 (Feb.) 1950.

The results show that some protection against histamine poisoning and exposure to cold is afforded within seven days by adrenocortical transplants to the dorsal musculature and against water intoxication within ten days.

JACOBSEN, Buffalo.

FAILURE OF SALT REPLACEMENT THERAPY IN ADRENALECTOMIZED RECENTLY CAPTURED WILD NORWAY RATS. CURT P. RICHTER, PHILIP V. ROGERS and CHARLES E. HALL, Endocrinology **46**:233 (Feb.) 1950.

The results of these experiments indicate that the recently trapped wild Norway rat has a much greater need of adrenal secretion than does its domesticated descendant.

It seems likely that the captured wild rat's greater chronic tension and more violent reaction to acute stimuli accounts for its higher need for adrenal secretion.

It appears that the domesticated rat is, so to speak, a creation of the laboratory worker. For this reason, the normal wild Norway rat may be the preferred animal for assays of the adrenal replacement therapies.

JACOBSEN, Buffalo.

ALKALINE PHOSPHATASES IN VARIOUS TISSUES OF THE RAT DURING THE ALARM-REACTION. MARC HERLANT and PAOLA S. TIMIRAS, Endocrinology **46**:243 (Feb.) 1950.

Distribution and concentration of alkaline phosphatase were studied in normal rats and in rats exposed to alarming stimuli (solution of formaldehyde U. S. P., cold and anoxia).

The rise in the alkaline phosphatase activity of the liver and lymphatic tissue appears to parallel the increased metabolism of these tissues during exposure to stress. Likewise, as there is a similar parallelism between the increased intensity of tissue phosphatases and endocrine activity, the observations presented here seem to indicate a close relation between this enzyme and cortical secretion during the alarm reaction.

JACOBSEN, Buffalo.

PSEUDOHYPOPARATHYROIDISM (SEABRIGHT BANTAM SYNDROME). CHARLES LOWE, ALBERT ELLINGER and WILLIAM WRIGHT, J. Pediat. **36**:1 (Jan.) 1950.

Pseudohypoparathyroidism, a very unusual disorder, is characterized mainly by failure of the appearance of phosphate diuresis after the intravenous administration of parathyroid injection. Along with this, the patient reported here presented hypocalcemia and hyperphosphatemia, elevated serum alkaline phosphatase and irregular calcification of the skeleton. This particular patient had a lifelong steatorrhea. The authors theorize that the associated absorption and metabolism of vitamin D and calcium was abnormal and that secondary hypocalcemia produced prolonged overstimulation of the parathyroid glands. They suggest that in this case, as a result of prolonged overstimulation, the kidneys have become refractory to parathyroid injection.

MACDONALD, Pittsburgh.

THYROID HYPERPLASIA IN RATS FOLLOWING THYMUS FEEDING. K. KJERULF-JENSEN, Proc. Soc. Exper. Biol. & Med. **66**:624 (Dec.) 1947.

In view of the observations of Hou (*Proc. Soc. Exper. Biol. & Med.* **43**:753, 1940), the author studied the goitrogenic effect of a soybean preparation. Five groups of rats were studied, weighing from 60 to 120 Gm. They were maintained on soybean flour, millet, sodium chloride, cod liver oil, ascorbic acid and supplements of dried thymus as well as the alcohol-extracted product, and also liver preparations. Rats were killed after thirty, sixty and ninety days. The author observed that feeding dried thymus elicited thyroid hyperplasia in the animals which were given the usual laboratory diet, as well as the soybean-millet diet. Administration of up to ten times as much thymus added but little to the increase in the size of the thyroid; however, the histologic changes, i. e., the cellular hyperplasia and especially the reduction of colloid substance, became particularly pronounced. The dried thymus was obtained from calves. The goitrogenic fraction was insoluble in water and ethyl alcohol. There was no goitrogenic effect from feeding dried ox liver, dried beef or dried cod spawn.

HANSEN, Galveston, Texas.

DYSONTOGENETIC PITUITARY CYSTS (PITUITARY CACHEXIA IN CHILDHOOD). H. S. BAAR, Arch. Dis. Childhood **22**:118 (June) 1947.

Two cases of pituitary cachexia in childhood are described. Both were due to large colloid cysts of Rathke's cleft, with pressure atrophy of the anterior lobe.

The designation "dysontogenetic pituitary cysts" for this type and a classification of the various pituitary cysts are proposed. The reasons that the designation "tumors of Rathke's pouch" for craniopharyngeomas is considered a misnomer are pointed out. The pituitary cachexia was associated with syringomyelia in one case and with fibrocystic dystrophy of the pancreas in the other. The possibility of a causal link between the latter and the pituitary disease is discussed.

KELLY, Milwaukee.

JUVENILE THYROTOXICOSIS TREATED WITH THIOURACIL. JAMES W. FARQUHAR, Arch. Dis. Childhood **23**:259 (Dec.) 1948.

A case of juvenile thyrotoxicosis is presented, and the results of treatment with thiouracil are recorded graphically over twenty-two weeks, with additional notes on progress since discharge from the hospital. The possibility of use of the drug as an alternative to surgical treatment in the prepubertal period is suggested, if similar therapeutic success is met with elsewhere.

KELLY, Milwaukee.

ADRENAL CORTEX AND ALLERGIC MANIFESTATIONS. E. ROMERO VELASCO, Schweiz. Med. Wchnschr. **79**:295 (April 2) 1949.

Desoxycorticosterone acetate (percoten®) was administered in iti water-soluble form intravenously and in its liquosoluble form intramuscularly. Among the 12 patients were 4 children 9 to 14 years of age with urticaria and itching, which in 3 responded well to the treatment. Some guinea pigs sensitized with serum could be protected against shock on further injection of serums by previous treatment with the drug.

AMBERG, Rochester, Minn.

Diseases of the Muscles, Bones, Joints and Lymph Nodes

CONGENITAL MULTIPLE EXOSTOSES IN FOUR SUCCESSIVE GENERATIONS. IHSAN DOGRAMACI, Ann. pædiat. **174**:203 (March) 1950.

Dogramaci presents and discusses a family tree exhibiting the occurrence of multiple exostoses in at least 11 persons in five generations among a total of twenty-one descendants of the original union.

FROM THE AUTHOR'S SUMMARY.

OSTEOMYELITIS FROM PARANASAL SINUSITIS IN CHILDREN AND PENICILLIN THERAPY. P. MEDA, Minerva Pediat. **2**:16 (Jan.) 1950.

Four cases of osteomyelitis from infection of the frontal or maxillary sinuses are reported. Three of the patients responded to penicillin therapy readily, but the fourth required also extensive operative treatment of the frontal bone.

HIGGINS, Boston.

THE IRON CONTENT OF THE BLOOD SERUM OF CHILDREN WITH MALIGNANT LYMPHOGRANULOMA. P. DE CAPRIO, Pediatria **58**:39 (Jan.) 1950.

Eight children with Sternberg's lymphogranuloma were found to have 25 to 66 micrograms of iron per hundred cubic centimeters of blood serum. These low figures are believed to be due to the storage of this element in the reticuloendothelial tissue.

HIGGINS, Boston.

Eosinophil Granuloma of the Bone. D. Vervat, Maandschr. v. kindergeneesk. **17**:385, 1950.

A short description of the etiology, pathogenesis, roentgen aspects and morbid anatomy of eosinophil granuloma in 2 cases is presented.

From the Author's Summary.

Unusual Cause of Sacral Pains in a Child (Spondylolisthesis). O. Priesnitz, Med. Klin. **16**:500 (April 21) 1950.

An 8 year old girl had pain in the region of the fifth lumbar vertebra for half a year. The pain was not made worse by moving or improved by rest. Extreme backward bending increased the pain. The spinous process of the fifth lumbar vertebra was sensitive to pressure and percussion. The pain was only slight, and without a roentgenogram it would have been declared psychogenic in all probability. On roentgen examination, a spondylolisthesis of the fifth lumbar vertebra was found. It is thought that a congenital spondyloschisis was responsible for the spondylolisthesis.

Amberg, Rochester, Minn.

Diseases of the Eye

Importance of Ocular Lesions for the Diagnosis of Embryopathies. A. Franceschetti and F. Bamatter, Bull. d. schweiz. Akad. d. med. Wissensch. **6**:201 (March) 1950.

Until the beginning of this century, congenital anomalies of the eyes were usually considered to be the consequences of congenital syphilis. As a result of progress made in the fields of experimental and human genetics, it is now known that in the majority of congenital defects of the eye, particularly in congenital cataract, heredity plays a preponderant role.

It is therefore all the more surprising that, as discovered by Gregg, congenital cataract can occur as the result of a rubella infection contracted by the mother at the beginning of pregnancy. In general, this cataract is accompanied with other anomalies (cardiac defects, deafness and oligophrenia, frequently with microcephaly, microphthalmia and dental anomalies and occasionally with deformities of the extremities) which closely resemble hereditary anomalies (phenocopies). Since a retrospective diagnosis of rubella is often problematic, it is all the more important to demonstrate that congenital defects of the eye exhibit certain characteristics which make possible the diagnosis of embryopathy due to maternal rubella with a fair degree of probability. In actual fact, in the majority of the 10 cases observed by us, we were able to confirm by anamnestic questioning of the mother the hypothesis of an embryopathy based on special features of the cataract (opacity predominantly axial with lenticular dysplasia) and frequent pigmentary changes in the fundus of the eye (pseudoretinitis pigmentosa). As a rule, hereditary cataract can be excluded by differential diagnosis (special nature of the lenticular changes, family occurrence, frequent consanguinity). This also applies to cataract caused by a toxoplasma infection occurring as a consequence of uveitis (posterior synechias). Other virus diseases besides rubella (mumps, chickenpox, etc.) can also cause an embryopathy, although much less frequently. Furthermore, it is becoming increasingly obvious that even purely exogenous factors (roentgen rays, avitaminosis, hormones) can be the cause of malformations. Although, according to Australian statistics, deformities following maternal rubella

may occur relatively frequently (almost 100 per cent), it is probable that the frequency of embryopathies due to maternal rubella is dependent on epidemiologic and geographic factors. Only after more precise investigations have been made, will it eventually be possible to discuss the problem of a medical and perhaps a legal indication for terminating a pregnancy in the early stages of which the woman contracts rubella.

From the Authors' Summary.

Cutaneous Diseases; Allergy

A Case of Acute Dermatomyositis. J. MacD. Holmes, Brit. M. J. **2**:511 (Sept. 11) 1948.

The author has given an excellent discussion of dermatomyositis, especially with regard to differential diagnosis and prognosis. This is done briefly and does not lend itself to abstraction.

Two severe attacks of dermatomyositis in a boy aged 15 are described. After many unsuccessful attempts to grow an organism from the blood and edema fluid Streptococcus viridans was obtained in pure culture from a biopsy specimen of muscle during the second attack. A piece of the excised muscle showed patchy inflammatory changes with perivascular cellular infiltration and necrosis of muscle fibers in several places. Only slight infiltration of arterial walls was seen in the sections examined. Complete recovery from both attacks occurred. The first responded slowly to penicillin alone and the second showed a slower response to larger doses of penicillin and sulfadiazine.

It is suggested that the severe symptoms were due to an allergic reaction in the muscles and skin to the Str. viridans infection and that a clinical and possibly an etiologic similarity exists among dermatomyositis, periarteritis nodosa, acute disseminated lupus erythematosus and erythema multiforme of the Stevens-Johnson type.

Birdsong, University, Va.

Xeroderma Pigmentosum. G. Calzetti, Clin. pediat. **30**:55 (Jan.) 1948.

A girl 4 years of age began to show the lesions of xeroderma pigmentosum when 2½ years old; the skin was covered with brown spots, was dry and appeared impetiginous. An ectropion involved each eye. The lesions were not improved by vitamin therapy, nor influenced by roentgen or ultraviolet irradiations. An attack of measles did not alter the condition. The capillaries of the skin were observed to be distended and irregular in shape.

Higgins, Boston.

Erythredema Polyneuropathy (Feer's Disease) and Mercury Medication. G. Fanconi and A. Botsztejn, Helvet. paediat. acta **3**:264 (Sept.) 1948.

In no less than 19 of 20 cases of erythredema polyneuropathy in the last eighteen months the children had been treated with mercury shortly before the commencement of the illness, either in the form of mild mercurous chloride U. S. P. (calomel) in worm powders or in the form of ointments containing mercury. This confirms our earlier view that erythredema polyneuropathy is a neuroallergic reaction to certain toxic substances, mercury acting also as an allergen (hapten). Administration of mercury preparations is probably the commonest cause of erythredema polyneuropathy in children constitutionally prone to it.

This conclusion is supported by the following findings: (1) positive skin reaction with mercury preparations and with calomel powder in fresh cases of

erythredema polyneuropathy; (2) demonstration of mercury in the urine; (3) rapid disappearance of symptoms following the elimination of mercury from the body by treatment with BAL (2,3-dimercaptopropanol); (4) the similarity in the patients' age group and their tendency to relapse in erythredema polyneuropathy (subacute allergosis) and calomel disease (acute allergosis). Since mercury can cause not only erythredema polyneuropathy and acute mercurial disease (calomel disease) but also polyradiculitis and lipid nephrosis, drugs containing mercury, and particularly chocolate calomel worm tablets obtainable without medical prescription, should be used with caution. FROM THE AUTHORS' SUMMARY.

PROGNOSIS OF ERYTHREDEMA POLYNEUROPATHY FROM EXAMINATIONS OF HISTORIES. R. F. LANDOLT and R. EGLI, Helvet. paediat. acta **3**:272 (Sept.) 1948.

Of 61 children who were hospitalized in the children's hospital of Zurich, Switzerland, between 1919 and 1935 on account of erythredema polyneuropathy, 34 were seen later. The following observations were made:

1. In 33 children the psychic development was completely unstriking. One child (female) had only a kleptomanic tendency. Her family showed a strong constitutional tendency.

2. Twenty-two children or 62 per cent showed a clear vegetative instability and 7 of them, or almost 5 per cent, increased blood pressure. It cannot be said with certainty whether the essential lesions are due to the contraction of erythredema polyneuropathy or whether a constitutional factor is involved whereby the disease is more easily acquired.

3. One child had hyperthyreosis with slight pituitary involvement.

4. Eleven children revealed in their anamnesis allergic disturbances, which were familial in 9 of them.

5. Six children died of erythredema polyneuropathy itself and 4 of an intercurrent disorder years later; there was no connection between their death and the disease under discussion. Among a further 121 patients with the disease observed in the years 1936 to 1948 there was only 1 death, or a rate of only 0.8 per cent.

6. Of all the patients (182) who have been observed so far, 5 contracted a frankly secondary disease, which ran a course sometimes less severe but often severer than the primary disease. FROM THE AUTHORS' SUMMARY.

CALCINOSIS INTERSTITIALIS UNIVERSALIS WITH ANGIOTROPHO NEUROSIS. H. ZELLWEGER, Helvet. paediat. acta **3**:287 (Sept.) 1948.

A 4 year old girl, with a volatile and emotional mentality, who had shown earlier trophic disturbances (including bedsores, appearing after seven days in bed) became ill with progressive muscular weakness, adynamia and sympathetic nervous symptoms; the cerebrospinal fluid had 38 mg. of albumin per hundred cubic centimeters. She showed sweating, tachycardia, hypertension (which later altered to hypotension) and a diabetic type of blood sugar curve, vasomotor disorders of the face and extremities, a lilac tinge of the face and a varying degree of edema; also there were mottling of the skin, thickening of the skin over the interphalangeal joints and trophic ulcers. She then displayed anorexia, muscular atrophy and generalized osteoporosis that gave rise to the spontaneous fracture of a femur a year later. By a series of roentgenograms made ten months later a generalized

interstitial calcinosis was observed, which has since become permanent, resulting in inability to move the hips and knees and the left elbow. Oscillometry of the brachial artery and changes of skin temperature demonstrated the poorness of peripheral circulation; masses of amorphous calcium and calcium phosphates and carbonates were deposited in the necrotic subcutaneous tissues. The blood chemical values, and especially those for serum calcium, were always found to be normal. The basal metabolic rate was normal. The cause was thought to be a central nervous lesion affecting the diencephalon, especially the vasomotor centers, which would account for the subcutaneous necrosis and calcification.

FROM THE AUTHORS' SUMMARY.

CAUSATION OF ERYTHEMA NODOSUM. G. MIESCHER, Schweiz. med. Wchnschr. **78**:269 (March 27) 1948.

The histologic examination of the lesions of erythema nodosum has shown that they consist of an acute leukocytic inflammation and are, for the most part, of large nodular granulomatous structure which, through its radial and palisade-like formation, produces a skin lesion of characteristic form and structure. These large nodules are resorbed giant cells.

The observations in these nodules contradict the previous conception that erythema nodosum is a single unit of one pathogenic origin. The author is of the opinion that it is a reaction phenomenon due to a variety of unknown causes. He states that in most cases the lesion is produced by disease processes other than tuberculosis, and he compares erythema nodosum to herpes simplex, which may be a manifestation of a variety of disease condition. In the initial stages of tuberculosis conditions are present which may produce erythema nodosum but the author states his view that other causes may act similarly to produce the erythematous lesion.

ABT and ABT, Chicago.

Miscellaneous

OBSERVATIONS ON THE USE OF PROCAINE-PENICILLIN. MERL J. CARSON, RUTH B. GERSTUNG and HERBERT A. MAZUR, J. Pediat. **34**:40 (Jan.) 1949.

Procaine penicillin (duracillin®) was given to children, 150,000 units to those under 11 Kg. of body weight and 300,000 units to those over this weight. A serum level of 0.1 to 0.2 unit per cubic centimeter can be maintained with this dosage at twenty-four hour intervals. Twelve hour intervals should be utilized when higher serum levels are desired. Penicillin given in this manner is rapidly absorbed, highly effective and infrequently produces toxic side effects. When sulfonamides are used concomitantly with penicillin, procaine penicillin is not the drug of choice because of the possibility that paraaminobenzoic acid derived from procaine may inhibit the activity of the sulfonamides.

MACDONALD, Pittsburgh.

AN OXYGEN-HUMIDITY-AEROSOL UNIT FOR INFANTS. J. C. RATHBUN and MARY E. SHUMAN, J. Pediat. **34**:80 (Jan.) 1949.

A portable plastic tent is described. It can be used as a humidifier, as an oxygen tent and as a vaporizer for administration of aerosol penicillin.

MACDONALD, Pittsburgh.

TOXICITY OF CARBONAMIDE. WENDELL DAVID and WALTER T. ST. GOAR, J. Pediat. **34**:83 (Jan.) 1949.

A patient with subacute bacterial endocarditis was treated successfully with penicillin and carinamide (4'-carboxyphenylmethansulfonanalide). Carinamide apparently produced fever, increased capillary fragility and increased bleeding time. These symptoms were controlled by administration of rutin.

MACDONALD, Pittsburgh.

SUSTAINED SUMMER HEAT AND FEVER IN INFANTS. HUGO M. CARDULLO, J. Pediat. **35**:24 (July) 1949.

Most children under 2 years of age have rising body temperatures when exposed to sustained environmental heat. This rise usually occurs about thirty-six hours after the beginning of exposure to environmental heat. Patients with diarrhea, however, may show fever within twelve hours, after the beginning of exposure to heat. Cardullo states that high fever is more apt to occur in these circumstances in children who have had a preexisting acute or chronic infection and in children with a congenital or acquired cerebral defect.

MACDONALD, Pittsburgh.

SUSTAINED SUMMER HEAT AND FEVER IN INFANTS. HUGO M. CARDULLO, J. L. J. KENNEDY, J. Pediat. **35**:43 (July) 1949.

In this study of 417 Minnesota children the rate of illness rose gradually during the first year. It was not influenced by sex. Respiratory disorders comprised 73 per cent of all illnesses observed. Peaks of respiratory disorders were in December and February and lowest levels were in June and July. Babies who had been breast fed had more illness in the second six months of life than babies who had been completely bottle fed. The authors note that other factors may be involved.

MACDONALD, Pittsburgh.

THE RESPONSE OF YOUNG INFANTS TO INGESTION OF AMMONIUM CHLORIDE. HARRY H. GORDON, HELEN MCNAMARA and HELEN R. BENJAMIN, Pediatrics **2**:290 (Sept.) 1948.

The results of observations on the effect of ingestion of ammonium chloride on the acid-base excretion of 3 premature and 3 full term infants are presented. Two of the 3 premature infants showed a definitely diminished excretion of ammonia and increased excretion of sodium as compared with the full term infants. The results suggest that some premature infants may have a renal tubular disability.

One of the 2 infants with diminished formation of ammonia and the third premature infant, the 2 smallest in the series, became listless, refused their feedings and showed depressed fontanels and diminished elasticity of the skin. This could not be correlated with changes in serum carbon dioxide content or chlorides or with the presence or absence of an adequate urinary formation of ammonia and conservation of sodium. Since the infants who became dehydrated gained weight while doing so, shifts of water and electrolytes from extracellular to vascular or intracellular compartments must have occurred. It is suggested that the tendency of young infants to disturbances of acid-base balance may be conditioned by disabilities in intracellular metabolism, as well as by renal dysfunction.

The implications of the limitations and variability in homeostasis for therapy are discussed.

FROM THE AUTHORS' SUMMARY.

OXIDATION OF PARENTERALLY ADMINISTERED C^{14} LABELLED TRIPALMITIN EMULSIONS. S. R. LERNER, I. L. CHAIKOFF, C. ENTENMAN and W. G. DAUBEN, Science **109**:13 (Jan. 7) 1949.

Palmitic acid was prepared containing radioactive carbon at the C_8 position and subsequently esterified with glycerol to produce tripalmitin. Particles 2 microns in size were made by emulsification with glycerol monostearate and with the help of supersonic energy. Twenty-five milligrams of tripalmitin was given intravenously to rats (132 mg. per kilogram of body weight). Evidence for the utilization of the parenterally administered fat was obtained by collecting the expired carbon dioxide, which contained 50 per cent of the administered radioactive carbon in the first twenty-four hours and by the fact that the remainder had been incorporated into the hepatic phospholipids.

FORBES, St. Louis.

SULFONAMIDE DRUGS AND THEIR ANTAGONISM. S. N. SANYAL, Indian J. Pediat. **15**:1 (Jan.) 1948.

The author concludes from experimental studies that the role of paraaminobenzoic acid in bacterial metabolism is not necessarily proved. It does antagonize the effect of the unsubstituted sulfonamide compounds but has no such effect on the substituted sulfonamide compounds.

MCGUIGAN, Evanston, Ill.

BONE MARROW FROM STERNUM, ILIUM AND TIBIA OF INFANTS. M. LATO, Clin. pediat. **30**:41 (Jan.) 1948.

Comparative findings on cytologic examination of bone marrow smears from the sternum, ilium and tibia of 10 infants are listed.

HIGGINS, Boston.

BIORHYTHMICS IN INFANCY: THE DAILY TEMPERATURE CURVE. C. IMPERATO and L. LANDUCCI, Lattante **19**:1 (Jan.) 1948.

The body temperature was taken every three hours over a period of one week; 8 breast-fed infants under 6 months of age and 6 infants between 7 and 12 months old receiving a cow's milk formula and vegetable soup were the subjects of the study. The feedings were given every three hours immediately following the taking of the temperature. The observations were made in May with the room temperature practically constant at 18 C. (64.4 F.).

The average temperature curves of the younger infants showed a high plateau between 6 a.m. and 3 p.m. (36.8 to 36.9 C. [98.2 to 98.4 F.]) and fell to a low point (36.5 C. [97.7 F.]) at 3 a.m. The average temperature curves of the older infants showed a high peak at 9 a.m. (36.9 C.), a lesser peak at 3 p.m. (36.7 C. [98.1 F.]) and its lowest point at 3 a.m. (36.5 C.).

HIGGINS, Boston.

SINGLE DOSE SULFONAMIDE THERAPY BY THE INTRAVENOUS ROUTE. C. IMPERATO and L. LANDUCCI, Lattante **19**:129 (March) 1948.

Twenty children with pneumonia were given a single dose of 0.24 Gm. of a sulfadiazine preparation per kilogram of body weight intravenously. The children responded satisfactorily to the treatment, the temperature becoming normal in 12 of them within twelve hours, in 7 others within twenty-four hours and in 1 within forty-eight hours. An appreciable blood concentration of the drug persisted for fifty-two hours in all but 4 of the children.

HIGGINS, Boston.

BLOOD CONCENTRATIONS OF SULFADIAZINE IN CHEMOTHERAPY. I. IMPERATO and L. LANDUCCI, Lattante **19**:225 (April) 1948.

Administration of 0.24 Gm. per kilogram of body weight of sulfadiazine intravenously to 14 children led to a mean blood concentration of the drug of 33 mg. per hundred cubic centimeters for a period of four hours. Administration by mouth of 0.35 Gm. per kilogram of body weight led to a mean concentration of 25 mg. per hundred cubic centimeters two to four hours later. Administration of 0.5 to 1 Gm. per kilogram of body weight per day led to a blood concentration of 22 to 36 mg. per hundred cubic centimeters so long as the drug was taken.

The following conclusions were drawn from the observations: Each child has an individual coefficient of absorption and blood curve applicable only to himself. The blood concentration does not increase in proportion to the amount of drug taken. The higher the blood concentration, the longer some of the drug will be present in the blood.

HIGGINS, Boston.

ACUTE POISONING BY ZINC PHOSPHIDE (Zn_3P_2). P. LUCIANI, Pediatria. **56**:299 (April) 1948.

A girl 17 months of age ate some mouse poison in the form of cereal grains coated with zinc phosphide. The next day she became ill, having extensive purpuric spots over the entire skin. She died five hours after her admission to the hospital. An autopsy revealed extensive hemorrhage into the brain, an enlarged spleen, fatty degeneration of the liver and myocardial involvement.

HIGGINS, Boston.

AXIAL TRANSVERSE STRATIGRAPHY IN PEDIATRICS. PIETRO AMISANO, Policlinico inf. (supp.) **16**:15 (Jan.) 1948.

The author applied the method of axial transverse stratigraphy on 3 boys 7 to 8 years of age, producing abdominal, thoracic, cervical and cranial stratigrams. They show the great selectivity of the new technics that allow one to obtain isolated transverse stratums free from images of the parts lying over and under them.

The application in childhood, besides confirming the results already obtained in adults, shows the ease of adaptability of the method to infancy, so that the results are likewise useful and worth consideration.

The author describes the fundamental principles of the new technics, the instruments used and the relation to preceding stratigraphic technics. As a practical demonstration, he presents some axial stratigrams wherein are visible the diaphragm, the mediastinal organs, the thoracic cavity, the cervical vertebrae and the frontal sinus.

FROM THE AUTHOR'S SUMMARY.

SERIOUS HYPOTHERMIA IN INFANTS. A. L. VELDKAMP, Maandschr. v. kindergeneesk. **16**:23 (Jan.) 1948.

Severe hypothermia below 30 C. (86 F.) is principally found between December and March. The signs are poor fluid intake, with dryness of the mouth, redness of face and extremities, cold skin, edema and slow pulse and respiratory rates (the respirations may be irregular). In the newborn child there are sometimes scleredema, hemorrhagic diathesis and convulsions. At autopsy other accompanying phenomena are found, such as infection or anemia with fatty degeneration of the internal organs. Occasionally, it was seen that pathologic changes existed in the thyroid and these were considered to be a manifestation of exhaustion of this gland.

The physiologic aspects of the failure in regulation of body temperature is as follows:

1. Chemical heat production is low in infants, owing to the small amount of muscular activity and the proportionately inadequate food intake. The poor development of the capillary system is associated with poor intake of oxygen in the lungs and poor liberation of oxygen to the tissues.

2. Physical heat loss, which is great in infants, is due to the relatively large body surface and to the thin and richly vascular skin.

The thyroid and adrenal glands are stimulated by low body temperatures, a stimulus which in turn causes increased glucose production in the liver. Oxidation in the tissues of the glucose thus formed leads to an increase in the rate of heat production. When there is a fall in the environmental temperature, it is observed that the temperature of the skin is affected before that of the other organs. The circulation is restricted to a minimum in order to conserve such heat as there is for the internal organs. In the presence of deficient oxygen, glucose or thyroid hormone, however, the metabolic rate is diminished and the temperature of these organs will also fall. With this fall in temperature there is a slower transfer of oxygen from the blood to the tissues, leading to further decrease in the metabolic rate and so on in a vicious circle.

Death from exposure to cold results from oxygen deficiency in the tissues. Infants with hypothermia in whom the internal body temperature is low must be treated by gradual stimulation of heat production, through administration of oxygen, glucose, thyroxin or epinephrine, by muscular activity or by feeding. If, however, only the skin temperature is below normal, one may cause the temperature to rise relatively quickly by the external application of warmth, e. g., warm baths and hot water bottles.

VAN CREVELD, Amsterdam, Netherlands.

EFFECT OF CARINAMIDE ON BLOOD CONCENTRATION OF PENICILLIN. MARIE R. H. STOPPELMAN, Nederl. tijdschr. v. geneesk. 93:90 (Jan. 8) 1949.

In the Children's Clinic of the Municipal University of Amsterdam, Netherlands, the effect of carinamide (4'-carboxyphenylmethansulfonanilide) was examined in 16 children. The serum concentration of penicillin was determined by the micromethod, described by Fleming in 1947, one-half hour, one hour and one and one-half hour after the intramuscular injection of the antibiotic. Then for forty-eight hours carinamide was given in a dosage of 0.4 Gm. per kilogram of body weight per twenty-four hours, and the penicillin determinations were repeated. For a control the determinations were preformed two days after the administration of carinamide had been discontinued.

Two of the 16 chidren showed no elevation in the penicillin content. In the other 14 children the concentration in the blood one and one-half hours after the penicillin injection was two to four times higher during the period of carinamide administration. In 5 of these patients the influence of carinamide was already demonstrable one hour after the injection and in 6 of them within one-half hour after the injection. Three of the 5 children with the highest elevation of the penicillin content of the blood had a disturbance in renal function. The greater penicillin level in those children might be founded either on the disturbance in the function of the renal tubules or on a less rapid excretion of carinamide via the glomeruli.

In 9 babies who received 10,000 units of penicillin orally every nine hours the influence of the administration of 0.4 Gm. of carinamide per kilogram of body weight per twenty-four hours was tested. Five of them showed a doubling of the

titer; in the other 4 babies the blood concentration of the penicillin was always lower than ⅛ unit per cubic centimeter. These 4 babies all were older than 5 months, an age at which less penicillin is resorbed from the intestine.

Finally, the penicillin content of the blood was determined in 2 children one-half hour and one, two, three and four hours after intramuscular injection of 10,000 units of penicillin. One and a half hour after the injection ⅛ unit per cubic centimeter was still present; when carinamide was administered simultaneously, this concentration was still found two and three hours after the injection. No toxic symptoms from the carinamide could be observed.

From the Author's Summary.

Newborn

Causation of So-Called Virus Diarrhea of the Newborn. J. D. Verlinde, Maandschr. v. kindergeneesk. **16**:385, 1948.

In the Netherlands in recent years epidemics of diarrhea among babies have been described in which no pathogenic bacteria could be demonstrated; it must be accepted that the etiologic agent was a virus. In 3 different epidemics of such a diarrhea, Verlinde has tried to isolate a virus. For this purpose he used defibrinated blood and suspensions of feces, filtered and unfiltered. Inoculations were performed in rabbits, guinea pigs, mice, young dogs, ferrets, hamsters and chick embryos. Morbid symptoms could be produced only in young ferrets at the age of 3 to 8 weeks. Eleven young ferrets, 3 weeks of age, who had been infected orally by fecal filtrates, contracted diarrhea and died after one to three weeks. The intestine of the dead animals was suspended, filtered and inoculated orally in 5 ferrets 5 weeks old; 4 of them died within four to seven days; the fifth became ill but recovered.

Then 12 ferrets at the age of three to six weeks were inoculated with filtrates of fecal suspension; three of them simultaneously received injections of convalescent serum. Of the last-mentioned 3 ferrets, 2 remained healthy; the third acquired diarrhea but recovered. The 6 nontreated ferrets and the 3 ferrets into which ordinary serum had been injected died after three to nine days. The observations at autopsy were degeneration of the epithelium of the mucous membranes of the intestine and mononuclear perivascular infiltrates in the liver. Animal experiments on a larger scale could not be performed on account of a shortage of young animals. Ferrets older than 8 weeks show either no morbid symptoms or a diarrhea from which they quickly recover.

The provisional conclusion is that these epidemics are caused by a virus. The possibility is considered of prophylactic treatment with convalescent serum in order to prevent this severe form of diarrhea.

Van Creveld, Amsterdam, Netherlands.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Philip C. Jeans, M.D., President

Katharine Dodd, M.D., Vice President

Sixtieth Annual Meeting, French Lick, Ind., May 9 and 10, 1950

Presidential Address: Application of Nutrition Research to Everyday Practice. Dr. Philip C. Jeans, Iowa City.

This paper was published in full in the September 1950 issue of the American Journal of Diseases of Children, page 363.

Pathogenesis of Megaloblastic Anemia of Infants. Dr. C. D. May, Dr. E. N. Nelson (by invitation), R. J. Salmon (by invitation) and Dr. C. U. Lowe (by invitation), Minneapolis.

This paper was published in full in the August 1950 issue of the American Journal of Diseases of Children, page 191.

DISCUSSION

Dr. Wolf W. Zuelzer, Detroit: I think Dr. May has answered a number of questions that have bothered my associates and me since the first clinical descriptions of this syndrome. The hypothesis which he has developed seems to me to be eminently reasonable. Slides were shown to bear out the idea that in some manner vitamin C deficiency potentiates a marginal deficiency in folic acid. That vitamin C deficiency in itself does not lead to megaloblastic anemia is clear from clinical observations and is also shown by Dr. May's animal experiments.

The four charts illustrated the effect of folic acid, vitamin B_{12} and vitamin C administered in varying combinations in four infants with megaloblastic anemia who also had clinical and biochemical evidence of vitamin C deficiency.

[Slide] The first chart was taken from data on one of our original patients. I might add that when we first started working with folic acid it took us about 10 cases to realize that we had to eliminate the possible effect of vitamin C, as the original patients routinely were receiving vitamin C on their admission to the ward. We learned from them that the administration of vitamin C before folic acid seemed to have practically no effect on hemopoiesis in fully developed megaloblastic anemia.

This patient received folic acid with a maximal response, although he was scorbutic and remained in a vitamin C-deficient state until he received ascorbic acid. On an attempt to apply the double reticulocyte test to this patient there was no further response, and the restoration of the function of hemopoiesis was complete.

[Slide] The second case showed much the same situation. After a complete response to folic acid, this patient had an infection, so that the hemoglobin concentration was not sustained. The ascorbic acid produced no further reticulocytosis, and it was only when a ferrous sulfate preparation (feosol®) was given that the patient had complete recovery.

[Slide] The third patient received vitamin B_{12} in what compared with amounts given to adults and the experience of others seemed to be ample dosage. There was no improvement and no reticulocytosis. He then received vitamin C, and there was still no response. Dr. May, in discussing this case with me, pointed out that the child had received sulfadiazine. Thus, it is conceivable that the intestinal flora, and therefore the folic acid content of the intestine, may have been altered. In any event, we then gave small amounts of folic acid, and a prompt reticulocytosis ensued, with a rise in hemoglobin concentration and red blood cell count. On further administration of vitamins B_{12} or C no effects were observed.

[Slide] The last slide showed what other investigators seem to have observed, and it threw an interesting light on some of the animal experiments of Dr. May and his associates. This patient received vitamin B_{12} at first, without response. Then he received vitamin C and had a response which at the time impressed us as good. However, after the reticulocytosis had subsided, the rise in red blood cell count and hemoglobin concentration still being moderate, we obtained much better response with administration of folic acid. This observation again suggests that the two substances, vitamins C and B_{12}, merely potentiated the residue of folic acid still present in the infant's organism. The folic acid deficiency was not completely cured, and hemopoiesis did not return to a fully normal state until folic acid was given.

Dr. Albert B. Sabin, Cincinnati: Dr. May and his associates have clearly shown that rhesus monkeys on a vitamin C-deficient diet acquire this interesting anemia. The point at issue appears to be the mechanism by which this anemia is produced. I rise to speak, not because of my hematological experience, but because many years ago I had an opportunity to make studies on rhesus monkeys with vitamin C deficiency (*J. Exper. Med.* **69**:507-516, 1939). I was much impressed with how sensitive rhesus monkeys are to vitamin C deficiency. Indeed, it appears that they probably are as sensitive as guinea pigs, if not more so, and it is doubtful whether certain changes which occur in rhesus monkeys with vitamin C deficiency occur in human beings.

I specifically have in mind my own observations of the fact that, on a great restriction of vitamin C, 52 per cent of 25 monkeys died of various types of infections within less than three weeks, while in a control group of 21 monkeys from the same shipment, receiving adequate amounts of vitamin C in the diet, in the same animal quarters, all but one remained well. Their whole bacterial flora was apparently upset. They had severe enterocolitis, pneumonia, cellulitis and so on, and it is noteworthy that these acute infections appeared before any gross signs of scurvy were discernible.

For that reason, I should like to ask Dr. May to comment further on his statement that infection did not appear to play a part in the pathogenesis of this special type of anemia. Even though his monkeys did not die, because it would appear that they showed scurvy only after about two months or more, and my monkeys displayed clinical scurvy within four to six weeks, is it possible that in his monkeys on a vitamin C-deficient diet there may have occurred sufficient change in the intestinal bacterial flora to contribute to the picture he has described?

Dr. A. Leonard Luhby, Columbus, Ohio: Dr. May has focused the attention of every one interested in this dyscrasia on the metabolic role of ascorbic acid.

I should like to show a slide concerning a patient with whom my colleagues and I have had experience which might add to what Dr. May has brought out.

[Slide] This slide showed the course of a 3 month old infant who came to the hospital with diarrhea. When the baby entered, she had 4,000,000 red blood cells and 12 Gm. of hemoglobin and was not anemic. She had had diarrhea for about 18 days. During an observation period we noticed that her red blood cell count fell, and after about 26 days it was about 3,000,000. At this point a bone marrow examination was done. The marrow was not especially megaloblastic. If one looked carefully, one might find some changes that might be called megaloblastic, but we gave the baby a transfusion at this point and brought her count up to 5,000,000 red cells and a normal hemoglobin concentration. Because this child was a foundling, we had the opportunity to keep her in the hospital for a longer period. We decided to follow her progress on the diets we had been studying. She was studied during January, February and March 1949, when we were testing various powdered milks and preparations which seemed to be indicated in the pathogenesis of this anemia. We had attempted to use vitamin B_{12} when it first was available and realized that it does not produce a remission of the disease. Of course, we came to appreciate that probably deficiency of folic acid was fundamentally involved.

This patient was given a basic formula of powdered milk; for the first 60 days she also received 50 mg. of crystalline ascorbic acid daily, plus members of the vitamin B and vitamin A groups. On this diet, which in our opinion at the time should have been adequate, the child's red blood cell count and hemoglobin concentration continued to fall, until the count reached about 1,800,000. During that time the patient's bone marrow was frankly and strikingly megaloblastic. We then gave the infant a crude concentrate of animal protein factor; she made an excellent reticulocytosis, and the red blood cell count and hemoglobin concentration rose.

This case shows the experience that might be expected with infants on such a regimen.

Dr. Arthur F. Abt, Chicago: I should like to point out that in attempting to produce anemia in scorbutic guinea pigs, Dr. Hans Aron found that only in young pigs weighing under 250 Gm. could he produce anemia.

As a second point, in working with these young scorbutic pigs in whom anemia had been produced, Aron observed that when iron was fed in the diet the plasma ascorbic acid level could not be raised. In other words, the iron acted antagonistically to the ascorbic acid. This was also seen to be true with other heavy metals—bismuth, arsenic and so on.

Before this Society some years ago I pointed out that in infectious diseases, particularly scarlet fever, no matter how much ascorbic acid is administered orally, the plasma ascorbic acid level apparently cannot be increased until the infection and fever are over.

Dr. Charles D. May, Minneapolis: In regard to Dr. Zuelzer's slides, I am particularly thankful for them because we have not had human material with which to verify our experimental results, and it is indeed gratifying to find the close correlation exhibited by the patients.

Concerning Dr. Sabin's remarks, I wonder whether the rate of growth in the monkey is not of some importance. Perhaps a 2 year old monkey is considerably further along his metabolic pathway than a 2 year old boy, and the monkey's rate of metabolism may be sufficiently higher to increase the requirements somewhat. However, we have found that with milks which contain as little as 1 mg. of ascorbic acid per liter, so that the animal may get only 0.5 mg. per day, it is virtually impossible to produce scurvy in these monkeys, unless the last traces

of ascorbic acid are removed by special measures, such as boiling or addition of copper ion. In that sense the monkeys do not seem to be more sensitive. Furthermore, two to three months were required for each of the monkeys to show scurvy.

Whenever they contract infections, I am sure they are as apt to become scorbutic as anyone else. Our animals did not have infections. Our colony was small; we had only the initial group of 15 or 20 monkeys. As with an infants' ward, one has much more trouble when conditions are crowded than when one has only a few. The monkeys were in individual metabolism cages, thoroughly scrubbed each day; we were most fortunate and had no trouble with infection. We know the symptoms of infection in monkeys because we have seen monkeys subsequently with dysentery, pneumonia and so on. It is safe to say, I think, that in these experiments any infections were not significant. The folic acid in the stools was the same in the anemic group as in the group that did not have anemia, so I do not believe the intestinal flora was altered significantly. That is another chapter which we will have to study later. The species of the monkey was quite different; so again I think there is no peculiarity in that regard. We had both cynomolgus and rhesus monkeys.

Dr. Abt's comments about young animals naturally appear germane. We also thought that might be important, and we had monkeys raised in laboratory conditions from birth, that were taken from their mothers as soon as they were born. We also worked with mature monkeys. It did not seem to make any difference whether they were young or older animals. Megaloblastic anemia occurs in the adult, as well as in the infant, when the scurvy has been severe enough and has lasted long enough. These animals all had iron added to their diets each day in adequate amounts, and the ascorbic acid was given in the same food; the ascorbic acid and iron did not seem to produce any interaction within the animal.

Transplacental Iron: Its Persistence During Infancy as Studied Isotopically. Dr. C. A. Smith, Dr. W. L. Caton (by invitation), Dr. C. C. Roby (by invitation), Dr. D. E. Reid (by invitation), Dr. R. S. Caswell (by invitation), and Dr. J. G. Gibson II (by invitation), Ann. Arbor, Mich.

This investigation began as a by-product of recently published obstetric research involving the repeated introduction of erythrocytes tagged with radioactive iron (Fe^{59}) into the circulation of 12 women during normal pregnancy. This provided the possibility of following 12 infants whose transplacentally acquired iron could be identified. In all but one of the 12 cord blood was secured for comparison with later specimens. The approximately four year half-life of the isotope has also permitted similar study of three more infants born at subsequent pregnancies, making a present total of 14 now investigated up to ages of 6 to 30 months. Another second infant and our first one representing a third pregnancy since introduction of isotope iron have been born within the past few days. All infants were born at full term; all of them and their mothers have been similar in diet, hygiene and general health to a random group attending the usual well baby clinic.

The total dosage of the isotope given in tagged cells during pregnancy ranged from 2 to 12 microcuries, equivalent to a total of 0.1 to 1.0 milliroentgen in the mother's blood stream. All the iron used was prepared in the Massachusetts Institute of Technology cyclotron. By the breakdown of donor cells, varying amounts of traceable iron were released into the general pool supplying both mother and fetus, so that each infant had at birth a basic index of isotopically active iron to hemoglobin or, presumably, of isotope iron to total iron.

[Chart] The first chart presented the changes of these activity indexes as compared with the index at birth. The method of calculation was shown. The index for each infant's cord blood was taken as 100 per cent. Since this cord blood index defined the ratio of isotope iron to hemoglobin at a time all the infant's iron was of transplacental origin, the degree of fall in indexes of subsequent blood samples measured the degree to which hemoglobin had been manufactured from other iron becoming available from the infant's diet or medication. Thus, a later blood sample with an index 50 per cent of that at birth would signify that half the hemoglobin in that sample was constructed from transplacental and half from postnatally acquired iron. The chart, which was plotted on a logarithmic time scale, indicated that such a point was reached about 18 months after birth.

The indexes departed little from the birth value during the first five to six months, after which a decline began, indicating the first significant utilization of dietary iron for formation of hemoglobin. By 2 years of age about 30 per cent of the hemoglobin was still formed from transplacentally acquired iron.

The total quantity of blood, of course, increases as the infant grows. Knowledge of the extent of this increase would allow us to calculate, at any sampling, the grams of total hemoglobin and the relative contributions of iron acquired prenatally and added postnatally. We did not feel it proper to ask the parents of these entirely well infants to allow a series of blood volume determinations and, therefore, have fallen back (unhappily) on the use of other workers' data to provide an approximation of the volume changes accompanying bodily growth. This is a singularly disturbing difficulty, not only because the literature indicates so large a degree of variation but also because no blood volumes have yet been published for the same group of infants from birth onward. The use of those at hand when our abstract was submitted for this meeting indicated an early emergence of transplacental iron from storage to a degree which we would now question. The large series reported yesterday by Dr. Fashena has given us a new basis of assumption regarding birth status, while the data assembled by Wetzel have been used for approximating the volumes to be expected after six months. We would—at present—prefer to offer no calculations between birth and that age. The charts, then, combine the best available blood volume predictions with the hemoglobin measurements and activity indexes from our own data and allow us to speak—admittedly without precision—of the later increases in total hemoglobin concentration and of their two sources.

[Chart] In chart 2, since all the hemoglobin in the cord blood was from transplacental iron, the symbols for the total circulating hemoglobin and for the transplacental iron composing it at birth have been superimposed at the arithmetical mean of 57 Gm. for the 14 infants. The range was indicated. No measurements were shown for the first six months, after which a general increase in total hemoglobin was indicated by the circles, and a widening gap (corresponding to the contribution of dietary iron) appeared between those symbols and the crosses representing hemoglobin from transplacental iron. Nevertheless, at the age of 2 years, from 60 to 90 per cent of the transplacental iron was still in use for hemoglobin. There were, however, decided individual variations, as the final charts showing the courses of three infants indicated.

The first child's infancy had been free of infections and his growth was rapid. His diet, and that of his mother while pregnant, was relatively high in iron. During this infant's first two years, the data suggested almost complete persistence of the high amount of transplacental iron which was in his blood at

birth. At 32 months nearly 75 per cent appeared to be in use as hemoglobin, although a noteworthy amount had been added, after his sixth month, from his diet.

The second child represented the opposite end of the performance scale. A small Negro infant from a poorly nourished mother, his indexes tended to decline fairly soon after birth, a fact which may have been associated with his own relatively high early intake of iron. At 2 years 60 per cent, and at 32 months only 40 per cent, of his somewhat meager original iron appeared to be in circulation as hemoglobin. The effects of his two severe infections were hard to assess, since other infants with at least as much infection have been better able to conserve their original iron.

Whether the original iron is removed entirely by excretion, or perhaps partially removed and temporarily stored, cannot yet be answered. Thus far, in four of the 14 infants we have evidence of decline followed by reappearance, which suggests temporary storage. This is shown in the final patient, in whom the low (and subsequently increased) level was observed during an acute infection at 20 months of age. At an earlier stage in this child's infancy, her family physician prescribed large doses of ferrous sulfate for at least 7 months, beginning three months after birth. It is of interest that the contribution of acquired iron nevertheless remained only moderate.

Although the radiation received by these fetuses and infants was calculated as about equal to that of cosmic radiation on persons living at sea level, numerous hematological examinations have been done to reveal any possible disturbances from that factor. Measurements of hemoglobin, erythrocytes and thrombocytes and total and differential white blood cell counts have been made for us by Dr. Diamond's laboratory. These values have all remained in ranges considered by him as normal and were similar to the ranges of a group of control infants. These examinations are to be continued, even though the initial radiation is steadily reduced not only by isotope decay but also by the dilution factor resulting from bodily growth.

Therefore, at the present stage of this project, we can report evidence that dietary iron makes only a negligible contribution to the hemoglobin of the usual infant during the six months following birth. On the basis of available evidence, from 60 to 90 per cent of the iron in hemoglobin at birth is serving the same purpose two years later. It is hoped that the accuracy of that estimate may be refined by our continued studies. In any case, the persistence of transplacental iron into later childhood will be easily measurable during the further growth of these infants.

Exchange Transfusion of Erythroblastic Babies with Blood from Female Donors. DR. LOUIS K. DIAMOND and DR. FRED H. ALLEN JR. (by invitation), Boston.

Analysis of the records of more than 650 infants with erythroblastosis fetalis seen at the Children's Hospital, the Boston Lying-in Hospital and the Richardson House, Boston, from Jan. 1, 1945 to April 2, 1950 has brought out new data of importance with respect to the treatment of this disease. It was shown in July 1949 that the use of blood from female donors for exchange transfusion had been associated with a significantly lower mortality rate than the use of blood from male donors. Since that time only blood from female donors has been given in exchange transfusion; while the mortality rate of 7.3 per cent with the use of blood from female donors is significantly lower than it had been

with the use of blood from male donors, the fact that no control series was run makes it impossible to draw any conclusions from the results in the last 109 infants receiving exchange transfusions.

It is now possible, however, to show a significant reduction in the incidence of kernicterus, from about 25 per cent in the days before exchange transfusion to less than 2 per cent in the 114 babies treated by exchange transfusion in the year ending April 2, 1950. The data from this analysis indicate that immaturity, which was probably the most important factor contributing to a high incidence of kernicterus in the earlier series, has been sharply reduced in the past year through a policy of not inducing labor, particularly before 38 or 39 weeks, in the sensitized Rh-negative woman. (Surprisingly, this policy has not resulted in an increased incidence of stillbirths or fetal hydrops.) This can be considered the most important reason for the reduction in the frequency of kernicterus. The data further show, for the first time, a significant decrease in kernicterus in erythroblastotic babies treated by exchange transfusion. Of no statistical significance because of the small number, but of great interest, is a group of 15 babies in whom a second exchange transfusion was given with the specific idea of preventing kernicterus. In all these babies the likelihood of kernicterus seemed to be high on the basis of history, laboratory evidence or clinical observation, and from past experience seven or eight of these babies would have been expected to show kernicterus. None did.

With the evidence that kernicterus has been notably reduced in frequency through conservatism, with respect to induction of labor and the liberal use of exchange transfusion in treatment of the babies, an attempt was made to explain the effectiveness of these two factors. The degree and duration of jaundice were found to be the common denominator. It was shown that kernicterus has occurred in 40 per cent of severely jaundiced erythroblastotic babies and is limited to seriously jaundiced babies whose jaundice does not begin to fade within the first five days of life; that severe jaundice is much more frequent in immature babies, and that the use of exchange transfusion greatly reduces both the severity and duration of jaundice. These observations suggest that blood pigments are of fundamental importance in the causation of kernicterus. They also suggest that pronounced or rapidly increasing jaundice in erythroblastotic babies is an important indication for exchange transfusion therapy.

DISCUSSION

DR. FRED H. ALLEN JR., Boston: From what Dr. Diamond has said you probably inferred that our thinking with respect to the causation of kernicterus has gone through another change, and that we have come back to the idea that the blood pigments may be the important factor. Any procedure which minimizes the extent or duration of the jaundice in these erythroblastotic babies can probably be expected to decrease the incidence of kernicterus, which I am convinced is far and away the most important of the complications of erythroblastosis.

Etiology of Kernicterus. DR. WOLF W. ZUELZER and DR. ROXIE T. MUDGETT (by invitation), Cincinnati.

A study of etiological factors in 55 consecutive infants with kernicterus seen at autopsy disclosed the existence of a large, seemingly heterogeneous group in which erythroblastosis fetalis was not a causative factor.

In 21 infants who had shown the characteristic features of erythroblastosis fetalis as regards family history, order number of pregnancy, racial distribution,

clinical symptoms, hematological findings and autopsy observations, the distribution of Rh types of mothers and infants was typical of erythroblastosis fetalis, and maternal isoimmunization against the Rh factor was readily demonstrated in 20 instances, the twenty-first having been studied before adequate technics were available.

By contrast the clinical features were not characteristic of erythroblastosis in a second group of 32 patients, which also differed from the first by its incidence of first-born infants and by a high percentage of Negroes. In 20 of these 32 infants studies of the Rh types of mothers and infants had been made, showing only one instance in which the combination of Rh-negative mother and Rh-positive infant was present. In no instance was it possible to demonstrate maternal Rh antibodies or sensitization of fetal erythrocytes. In the majority of the cases tested, mother and infant were compatible in regard to blood group ABO. The incidence of incompatibility between mother and child in the ABO system was higher than expected in this group but of questionable statistical significance. In no instance was it possible to demonstrate unusually high agglutinin titers or immune antibodies against groups A or B in the maternal serum.

Prematurity, severe infections, diarrheal disease, pulmonary and cerebral hemorrhage and maternal diabetes were the chief conditions encountered in those cases of kernicterus in which erythroblastosis fetalis was excluded.

The conclusion was reached that kernicterus does not represent a specific entity. The observations presented support the hypothesis that the phenomenon results from the coincidence of nonspecific injury to certain parts of the newborn brain with hyperbilirubinemia.

DISCUSSION

DR. IRVING J. WOLMAN, Philadelphia: Traditionally, to the pathologist kernicterus has meant a yellow staining of the nuclei of the brain. This need not be limited to the ganglions but can be observed in foci of the cerebral cortex and in various parts of the spinal cord and medulla. There has been a growing tendency in the past few years for the term kernicterus to be transferred by the clinician to apply to the cerebral symptoms observed in children who have recovered from erythroblastosis.

When a child has died from almost any disease, certain nonspecific changes are demonstrable in the viscera. Such lesions are known as cloudy swelling, parenchymatous degeneration, fatty changes in the liver and fragmentation of the heart muscle. Often when the brain is studied, one can find the same sort of degenerative changes in the cerebral cells. Such children usually died of infection, but not necessarily. I have seen the same nervous system changes in children who died of diarrhea and other disturbances. The large cells of the brain do not look quite right. They have lost their Nissl substance; they are shrunken, and they obviously have been injured. There is always the question of whether such nerve cell changes are reversible; that is if the youngster had not died from his illness, would many or all of these affected brain cells return to normal functioning?

In Dr. Zuelzer's series there were only about 15 per cent that were clinically jaundiced; yet at the postmortem table jaundice was demonstrable in the brains of every infant. Were the data incomplete in the sense that jaundice was not recorded on the clinical charts unless it was the chief symptom? Perhaps if these children had the type of change I mentioned, along with the subclinical icterus and slight elevation of the bile pigments, the injured cells picked up these pigments and, therefore, stood out.

Is it justifiable to separate out these cases because of their appearing in the newborn period? The change I referred to is seen in children of all ages.

Dr. Wolf W. Zuelzer, Detroit: Dr. Wolman raised some important questions. I deliberately tried to avoid the question of pathogenesis because I think that until much more painstaking effort is made to study the newborn brain histopathologically we will not know the answer.

I should like to say, in passing, that several of the patients did not have clinical jaundice at any time, and even at autopsy none of the other organs was visibly jaundiced. That is not to say they did not have hyperbilirubinemia. The majority were icteric, but in the majority of the infants of group 2 the icterus was no greater than that ordinarily classified as physiological jaundice, especially in a premature infant.

As to the histopathological changes that Dr. Wolman mentioned, it is my tentative opinion, from the material that we have seen, that he is correct and that the staining is merely the accidental gross revelation of a change which may occur in a nonicteric patient.

There is one interesting report on an adult brain, the only adult case I am familiar with that resembles kernicterus, in which a patient with arteriosclerotic changes in the brain and simultaneous obstruction of the bile ducts from a carcinoma showed comparable lesions in those areas. Therefore, I believe the inference can be drawn, but at present it is only an inference.

Studies on Spontaneous Hypoglycemosis: The Place of Pituitary Adrenocorticotropic Hormone (ACTH) in Therapy. Dr. Irvine McQuarrie, Dr. M. R. Ziegler, Dr. E. G. Bauer (by invitation) and Dr. W. S. Wright (by invitation), Minneapolis.

Metabolic studies and clinical observations were made before, during and after a four day period of intensive administration of ACTH in eight patients suffering from severe spontaneous hypoglycemosis and in one control subject. The experimental subjects consisted of a 6 week old infant with subdural hematoma, a 56 year old woman with multiple small pancreatic beta cell adenomas, an 11 year old boy with Addison's disease of severe grade and five children (aged 1 to 6 years) with "familial hypoglycemosis." Special tests for adrenal cortex, anterior pituitary and hepatic functions revealed no evidence of disease in the corresponding organ systems, except for obvious cortical deficiency in the patient with Addison's disease.

The woman and two of the patients (brother and sister) with familial hypoglycemosis had previously been subjected to partial pancreatectomy (approximately 85 per cent removal) with only temporary improvement. The pancreas of the woman showed several small beta cell adenomas. The only abnormalities of the pancreas of the two children was a total or almost total absence of alpha cells in the islets and a striking loss of cytoplasmic granulation in the beta cells. These surprising histological deficiencies were made evident by use of Gomori's stain. Such cases may represent a heretofore unrecognized entity in which deficiency of the hypoglycemic factor in the alpha cells is responsible for the spontaneous hypoglycemosis.

The type of metabolic response to ACTH on the part of the hypoglycemic patients, other than the one suffering from Addison's disease, was similar in all respects to that of normal subjects. However, under the conditions of this study, instead of producing a transient state of diabetes mellitus, as it does in the normal subject, the ACTH merely abolished the hypoglycemosis temporarily.

All symptoms and signs characteristic of the hypoglycemic state disappeared completely and remained in abeyance so long as the hormone was given. The electroencephalogram was likewise restored to normal.

One of the most severely afflicted patients in the series was maintained in an essentially normal state on a greatly reduced dosage of ACTH for more than a year. No evidence of refractoriness to ACTH was observed, and no undesirable effects from its prolonged use were ever noted. The therapeutic response of patients with nonaddisonian spontaneous hypoglycemosis to this hormone is comparable to that of persons with pancreatic diabetes to insulin.

Composition of Meconium: Isolation of Blood Group–Specific Polysaccharides; Abnormal Composition of Meconium in Meconium Ileus. DR. SAMUEL RAPOPORT and D. J. BUCHANAN (by invitation), Cincinnati.

As you well know, meconium, the first intestinal discharge of the newly born, differs in appearance and properties from the stools of later life and represents the material accumulated during fetal life. It is free of bacteria or their breakdown products; it is blackish green and odorless, has a viscid, sticky consistency and varies in amount from 60 to 200 Gm. It is first demonstrable during the fifth month of gestation. Generally, it has been considered to be an accumulation of debris consisting of desquamated cells of the alimentary tract and skin, lanugo hairs, fatty material from the vernix caseosa, amniotic fluid and various intestinal secretions. Its color probably is due to bile pigments. In infants with meconium ileus the amount of meconium is greater and its consistency even more viscid than normal. This disorder frequently represents the earliest and severest form of cystic fibrosis of the pancreas, a disease characterized by diminution or absence of pancreatic enzymes in the intestinal tract. Surprisingly enough, neither normal nor abnormal meconium has as yet been studied by modern methods. It appeared of interest to embark on a study of their chemical composition.

[Slide 1] This slide listed the composition of a pooled sample of normal meconium, as well as that of a specimen obtained from an infant with meconium ileus. In regard, first, to normal meconium, compared with adult stools, the water content was high and the ash content extremely low. The nitrogen, even on a dry weight basis, was low and, for the most part, soluble in water and trichloracetic acid. No protein could be demonstrated on heating or by the usual precipitants. Relatively little lipid material, about 10 per cent, was present. The most prominent component appeared to be a polysaccharide, which yielded a reducing sugar after acid hydrolysis. These data are incompatible with the prevailing ideas about the composition of meconium as a chance collection of debris; they indicate the presence of a specific component, carbohydrate in nature, as a consistent major constituent.

The meconium from the patient with ileus differed greatly in composition from the normal. It was much higher in nitrogen, which, for the most part, was precipitable by trichloracetic acid. The qualitative protein reactions were positive. The percentage of carbohydrate was relatively low. The absolute amount, however, may well have been normal; although a quantitative collection was impossible, it appeared that the amount of meconium was much greater than usual.

The next phase of the study was directed toward elucidation of the nature of the carbohydrate. It appeared to exist in combination with nitrogenous substances and to represent a mucopolysaccharide. The polysaccharide was water soluble and precipitable by 10 volumes of glacial acetic acid or 5 volumes of ethyl alcohol. It was not precipitated by various deproteinizing agents. Most of the bile pig-

ment could be removed by acetic acid, alcohol or treatment with barium hydroxide and zinc sulfate. The solutions of the polysaccharide were translucent, with a light yellow or greenish tinge. The reducing substance was nonfermentable. Specific color reactions were positive for glucosamine, galactose and methylpentose. Mucic acid could be isolated. Hexuronic and sulfuric acids were absent. The general similarity of the polysaccharide to blood group substances prompted the investigation of the blood group activity of meconium.

The activity of meconium was assessed by its ability to inhibit isoagglutination, according to the procedure of Morgan and King, with 20 to 40 agglutinating doses of human anti-A or anti-B serum. It was observed that a sample representing a pool of 25 meconium stools neutralized both A and B agglutinating serums in amounts of 25 and 300 micrograms, respectively. The next step was to determine whether the activity of the meconium of an individual infant's stool corresponded to his blood group and whether a distinction existed between "secretors," i. e., infants whose body secretions contain water-soluble group-specific substances, on the one hand, and nonsecretors, i. e., infants whose body fluids lack this property, on the other. This property, by the way, is genetically determined. Individual samples of meconium, blood and saliva from a group of 69 infants were tested.

[Slide 2] The slide presented the relevant data. Whenever blood group activity was present in the saliva, indicating the secretor characteristic, the same activity was present in the meconium. The activities were of remarkable degree. As little as 0.05 microgram of meconium from either A or B secretor babies was sufficient to inhibit completely the agglutination of the red cells. The activity of the meconium from the 2 infants of group AB was considerably lower, less than 1:100. Meconium from infants of group O was, of course, devoid of human blood group activity. A further study of the chemical properties of the blood group substances prepared from individual infants indicated close chemical similarity among the polysaccharides whether or not blood group activity was present and regardless of the blood group type. From the analyses of the purified products and of crude meconium, one may estimate that the polysaccharides account for as much as 80 per cent of the dry weight of meconium. We have had the opportunity to examine the meconium of puppies and of a calf fetus. Both crude products had a considerably lower polysaccharide content, which, however, when purified resembled human polysaccharides closely. They were devoid of human blood group A or B activity.

The observations reported are as yet of a preliminary nature and require elaboration in several directions. From the present data it appears that meconium in the first instance represents the residue of the mucous secretions of the entire alimentary tract, including saliva and gastric and intestinal juices. It is known that in secretors the secretions of many glands normally contain mucoproteins and exhibit blood group activity. The absence of protein from normal meconium may be attributed to the activity of proteolytic enzymes, the foremost being tryptase, which digests the protein while leaving the polysaccharides intact. The different composition of the meconium from the infant with meconium ileus might then be due to the lack of proteolytic activity, which would lead to the persistence of protein. The much greater than normal viscosity of meconium of infants with ileus would find its explanation in the circumstance that mucoproteins are more viscous than mucopolysaccharides. One may wonder whether the well known viscosity of bronchial secretions and other mucous secreta of the body, so characteristic of fibrocystic disease, might not reflect a widespread lack of proteolytic

activity which normally may serve to reduce the viscosity of mucus. The observations on calves and dogs indicate that the occurrence of polysaccharides in meconium is not restricted to man.

The availability of a potent and easily accessible source of human blood group substances in the form of meconium appears of great theoretical and practical interest. It opens the possibility of study of hitherto almost inaccessible blood group substances and of a close comparison between human and animal products. Blood group substances from meconium offer great promise in blood transfusion practice as neutralizing agents of agglutinins of pooled plasma or blood, with the advantages over currently used products of high potency, simple purification and certainty of absence of antigenic properties for man.

Significance of Altered Viscosity of Duodenal Content in Pancreatic Fibrosis ((Mucoviscidosis). Dr. Harry Shwachman (by invitation), Dr. Paul Patterson (by invitation) and Dr. Sidney Farber, Boston.

The most direct method of establishing a diagnosis of pancreatic fibrosis is considered to be the demonstration of absent or greatly reduced trypsin activity of the duodenal contents. We should like to supplement the diagnostic criteria by emphasizing the alterations in the viscosity or physical state of the fluid as measured by the Ostwald viscosimeter.

In discussion of pathogenesis the term "mucoviscidosis" is preferred in the light of the nature of the mucous secretion and the concept of a generalized disease.

The results of the measurements of the viscosity of the duodenal contents were presented in patients with mucoviscidosis and in normal and sick persons. These observations were correlated with the trypsin activity in the duodenal content and the clinical condition of the patient. The effect of time on the increased viscosity of the duodenal fluid was mentioned. Three case reports with pathological studies were presented. In these patients the duodenal fluid during life showed normal trypsin activity but altered viscosity. According to our previous criteria, the diagnosis would not have been made in these patients. In two of the patients there was notably increased viscosity. We propose the measurement of the viscosity of the duodenal contents as an important adjunct in the evaluation of a patient suspected of having mucoviscidosis.

DISCUSSION

Dr. Dorothy H. Andersen, New York: All of us who have had experience with patients having fibrocystic disease have known trouble in duodenal intubation. My associates and I, and other observers with long series of cases, have seen a few instances in which presence of trypsin was demonstrated by gelatin methods, but the patient had fibrocystic disease both clinically and on postmortem examination. In our series there are three that I accept as having had a higher trypsin level than would seem compatible with the diagnosis.

One of these cases interested me especially; a young infant had a fair amount of trypsin at 1 month, much reduction at about 3 months and none at 5 months. This gives one example, at least, of a progressive decrease in early infancy.

Dr. Shwachman's paper brings up two questions concerning the reason for the variability in age of onset and clinical picture. One is exemplified by the case just mentioned in which pancreatic function progressively deteriorated in early infancy. It is possible that this may infrequently occur later in childhood. There may be instances in which the lesion is only partial at birth but progresses to completion during the first few months of life.

The other question concerns whether there are instances of a partial deficiency that continues to be static. I have not seen such a case of which I have been certain, although it is perfectly possible, to the best of my knowledge.

We have to thank Dr. Shwachman for several attempts to produce relatively simple methods of making the diagnosis of fibrocystic disease; that is, simple as compared with duodenal intubation. These have included the gelatin film test and the amino acetic acid (glycine) method; other persons also have made such attempts. However, at the moment there is no absolute test that I know of that will be uniformly satisfactory throughout a long series, and the problem of methods of diagnosis is still open.

I am unable to restrain myself from commenting on the term "mucoviscidosis," though I probably should not do so. I think that the use of this word has the semantic ill effect of giving one the illusion that the basic causation of the disease is known. It is possible but not proved that the pancreatic and pulmonary lesions rest on the same mechanism, and until proof is forthcoming I prefer to keep an open mind.

Infectious Nature of Exanthema Subitum (Roseola Infantum). Dr. Edward B. Shaw, Dr. C. Henry Kempe (by invitation) and Dr. Henry K. Silver (by invitation), San Francisco.

Exanthema subitum is the only remaining exanthematous disease of childhood in which the causation has not been established. Since the disease was first described by Zahorsky in 1910, it has been considered to be due to an infectious agent, probably a virus. Many have believed, however, that the underlying infection might be caused by a number of different agents, the characteristic rash being a response which is conditioned by the host rather than by the nature of the pathogen.

This disease occurs primarily in children between the ages of 6 months and 2 years and is extremely common, but there is usually lacking a definite history of exposure to other children who are similarly affected. Descriptions of the epidemic occurrence of the disease are at variance with the common occurrence of the infection in children who have no history of exposure to persons with proved attacks of this infection.

In the experimental study blood was withdrawn from a child with this disease on the second day of fever, and immediately thereafter 1 cc. of bacteria-free serum from this blood was injected intravenously into a 6 month old subject with no previous history of illness, in whom permission for the transmission of this mild illness was provided. Nine days after the intravenous injection of the serum the recipient showed the typical course of infection with a three day fever. The infant was never especially ill. There was early leukocytosis with a subsequent pronounced leukopenia and enlargement of the suboccipital nodes. A typical maculopapular rash appeared immediately following a subnormal drop in temperature. The eruption in the 18 month old donor was definite but fleeting and persisted about four hours. The eruption in the recipient was quite prominent and persisted for approximately 12 hours. This rash was demonstrated by kodachrome® pictures.

This experiment substantiates the infectious nature of this disease and supports the veiw that a virus is the etiological agent. Attempts to infect numerous monkeys by a similar inoculation experiment have met with fairly uniform success in the production of fever five days following subcutaneous inoculation. Chick embryo inoculations have not been completely convincing, but the death rate in

inoculated embryos following initial inoculation and the transmission of serial passage material has suggested a lethal effect to support the view that an infectious agent has thus been perpetuated.

This material permits some discussion of the production of disease in the period of infancy, which is characterized by zero immunity and maximum susceptibility, by an agent which must be ubiquitously distributed among healthy human beings, resistance at a later age being due either to inapparent infection in infancy or, more probably, to the acquisition of nonspecific insusceptibility at a later age.

DISCUSSION

Dr. William L. Bradford, Rochester, N. Y.: Several years ago Dr. Breese Syverton inoculated bacterially sterile nasal washings from children with early exanthema subitum into a number of different species (rabbits, guinea pigs and mice) with negative results. Dr. Shepard inoculated the chorioallantoic membrane of the chick embryo with serum from patients with the early disease with similar negative results.

Because the German authorities suggested a possible relation between exanthema subitum and influenza, my colleagues and I collected early and convalescent serums from patients with the disease, which Dr. Searle tested for complement-fixing antibodies against mouse lung antigens of types A and B influenza viruses. In no instance was an antibody against these two races of influenza virus demonstrated.

Dr. A. Ashley Weech, Cincinnati: Locating volunteers during infancy presents the investigator with an experimental enigma which often seems to block entirely his efforts to carry studies of the transmission of disease ahead. It might be worth pointing out that at present a therapeutic indication exists for finding out what febrile diseases attended by rashes will do to infantile nephrosis. I suggest to Dr. Shaw that this group of babies might benefit by having exanthema subitum transmitted to them.

Dr. Edward B. Shaw, San Francisco: I should like to express my gratitude for the last suggestion.

Antipoliomyelitic Substance in Milk of Human Beings and Certain Cows.
Dr. Albert B. Sabin, Cincinnati.

The present investigation was undertaken to obtain data that could be used in evaluating the role which prolonged breast feeding, still practiced in many parts of the world, might play in keeping down the incidence of paralytic poliomyelitis. It was also deemed desirable to know something of the content of antiviral substance in breast milk, because it can coat the portal of entry of poliomyelitis virus in the alimentary tract.

Milk and blood were obtained simultaneously from 30 mothers—from 10 during the first five days after delivery, from eight between 38 and 87 days and from 12 between 101 and 340 days. The serum and milk were tested simultaneously against the Lansing strain of poliomyelitis virus by intracerebral inoculation of the mixtures in mice. The relative concentration of the protective substance was tested by mixing various dilutions of the serum or milk with a constant amount of the virus (approximately 50 median lethal doses). All the samples of serum and milk from 25 of the 30 mothers were capable of neutralizing the virus. All 10 milk specimens obtained between two and five days after delivery, and 15 of the 20 obtained 38 to 340 days after delivery, exhibited antipoliomyelitic activity. It is noteworthy that approximately 80 per cent of the milk specimens

obtained between 101 and 340 days after delivery, i. e., at a time the placentally transmitted antibody had mostly or entirely disappeared, still contained varying amounts of neutralizing substance for the virus of poliomyelitis. With one exception, the titer of the antipoliomyelitic substance (i. e., the dilution at which 0.03 ml. still protected against 50 median lethal doses of the virus) ranged between 13 and 64 in the milks obtained two to five days after delivery and between 2 and 14 in those obtained after 38 to 340 days. However, no correlation was noted between the titer of antibody in the serum and of the antipoliomyelitic substance in milk, although both proved to be resistant to heating at 60 C. (140 F.) for 30 minutes. Since these data suggested, without being finally conclusive, that the antipoliomyelitic substance in milk was not antibody, eight selected milk and serum specimens were also tested against the virus of Japanese B encephalitis. While all the serums were negative, seven of the eight milk specimens had protective substance for the Japanese B virus. However, different factors were apparently involved in the effect against these two viruses, since the most potent antipoliomyelitic milk specimen failed to protect against the Japanese B virus, and two milk specimens without activity against the poliomyelitis virus were effective against the Japanese B virus. Similar tests on the milk obtained separately from nine cows showed that an antipoliomyelitic substance was definitely present in only two.

These observations have little significance for a virus whose portal of entry is not the alimentary tract. With poliomyelitis, however, it becomes necessary to consider the role that breast feeding beyond the third month, or the drinking of "antipoliomyelitic" cow's milk, might play in preventing or modifying the infection in human beings.

Excretion of Poliomyelitis Virus: Experimental Observations. Dr. Harold K. Faber, Rosalie J. Silverberg (by invitation), Dr. Lester A. Luz (by invitation) and Luther Dong (by invitation), San Francisco.

In human poliomyelitis virus appears in the pharynx and stools several days before the onset of symptoms. Its source and route of exit have remained obscure. Does it come from infected surface epithelium or from inner foci of infection (peripheral ganglions, central nervous system)? Does it reach the surface through vascular or lymphatic channels or through the peripheral fibers of the nerves themselves?

Monkeys, mainly cynomolgus, were inoculated with poliomyelitis virus (Cam and Wis 1944 strains) in groups of four, each group at one of the following sites: (1) the central end of the divided right infraorbital branch of the maxillary division of the fifth cranial nerve; (2) the right gasserian ganglion; (3) the brain (thalamus); (4) the celiac ganglion. Pharyngeal washings and stools were tested for virus thereafter, and, after killing the animals, the brain stem and cord were examined histologically. From washings and/or stools virus was recovered repeatedly in all four types of experiment, as a rule early and before the onset of symptoms of poliomyelitis. In some instances after peripheral inoculation, it was recovered from animals showing no histological evidence of infection of the central nervous system but in which virus was demonstrable in the gasserian ganglions. Control experiments in which large amounts of virus were introduced into the blood stream gave negative results.

The bearing of these experiments on the questions raised in the first paragraph was discussed. Primary infection of the mucous membranes can be ruled out. Excretion through the blood and lymphatics to the surfaces of the respiratory and alimentary membranes appears unlikely. Excretion by way of the peripheral

nerve fibers by centrifugal spread seems to be the preferable explanation. Allowing for the technical difficulties of detecting virus in the scanty secretions of the pharynx, it seems possible that (excepting perhaps after celiac inoculation) the primary place of excretion of virus in these experiments was the pharynx and that its presence in the stools may have been due to the swallowing of pharyngeal secretions.

Use of Systemically Administered Penicillin as a Prophylactic Against Ophthalmia Neonatorum. Dr. Lewis K. Sweet,† Dr. Robert H. Barter (by invitation), Dr. Pete Commings (by invitation), Dr. W. M. Featherstone (by invitation), Dr. G. F. Parker (by invitation), Dr. Raney Oven (by invitation), Dr. J. P. Fairchild (by invitation), Dr. John F. Mohr (by invitation), Dr. Joseph J. McDonald (by invitation) and Dr. Robert T. Miller (by invitation), Washington, D. C.

A study was made in the Gallinger Municipal Hospital between Oct. 1, 1948 and Dec. 31, 1949 to determine the value of a single intramuscular dose of 50,000 units of crystalline penicillin as a prophylactic agent against ophthalmia neonatorum. Alternate newborn infants received the usual Crede prophylaxis with 1 per cent silver nitrate solution; the remainder received penicillin intramuscularly. The eyes of all infants were irrigated with boric acid solution an hour after the prophylaxis.

Random blood samples drawn within the first 12 hours of life showed that the infants maintained a high blood concentration of penicillin for at least 12 hours after the injection of penicillin.

There were 5,919 infants included in the study, of whom 2,586 received penicillin and 3,159 received silver nitrate; in 174 both drugs were given or the drug used was not recorded on the chart. There were 46 ocular reactions (1.78 per cent) among the 2,586 penicillin-treated infants. These included seven cases of gonococcic conjunctivitis, 26 cases of nongonococcic bacterial conjunctivitis and 13 cases of transient nonbacterial conjunctivitis. There were 141 (4.46 per cent) ocular reactions among the 3,159 infants who received silver nitrate. These included six cases of gonococcic conjunctivitis, 51 cases of nongonococcic bacterial conjunctivitis and 84 cases of transient nonbacterial (chemical) conjunctivitis which lasted over 24 hours. By the chi-square method, the differences in the incidence of total reactions and transient nonspecific reactions are highly significant (chi-square = 32.8 and 17.87, respectively) and the difference in the incidence of total reactions and nongonococcic bacterial conjunctivitis is significant (chi-square = 4.01). The difference in the incidence of total reactions and of gonococcic conjunctivitis is not significant.

Intramuscular administration of penicillin, as used in this study, seems to be as effective as silver nitrate therapy in reducing gonococcic conjunctivitis, appears to be more effective in preventing nongonococcic bacterial conjunctivitis and eliminates almost entirely the transient nonbacterial conjunctivitis.

DISCUSSION

Dr. Stewart H. Clifford, Brookline, Mass.: We are indebted to Dr. Sweet for investigating this important problem. Penicillin appears to be as effective a prophylactic as silver nitrate. It is disappointing to Dr. Sweet and to all of us that penicillin could not be demonstrated to be distinctly superior in preventing gonococcic infection. The problem we are faced with is an inherited one of

† Dr. Sweet died Sept. 23, 1950.

tradition and state law, which in most areas demands silver nitrate treatment in all newborn infants or, as is usually written in the state laws, "some other equally effective treatment."

Thus far, evidence has not been accumulated to the point that the state health departments have felt free to relinquish the old law requiring silver nitrate therapy and allowing use of penicillin instead. We hope that studies such as Dr. Sweet has reported can be carried out in large clinics in other areas where gonococcic infection is a problem, in the hope that soon evidence will be strong enough to convince all that we can abandon the silver nitrate regimen. The number of areas where mass experiments can be carried out is limited. In our region, to accumulate the number of cases of gonococcic infection that were seen in this study would take 15 or 20 years because of the low incidence of the infection. I think there is an obligation, while gonorrhea still exists in certain areas and before it is all stamped out, for other large clinics to make a convincing study; otherwise we will be giving silver nitrate to our great-grandchildren.

In order to lay once and for all the conception held in some places that penicillin is not excreted in effective levels into the eye or the tear fluids, I should like to ask Dr. Sweet whether, in his studies of the penicillin level, it was possible to make any actual determination of the level either in the purulent discharge or in the watery secretions of the eye.

With the more effective means of treating gonococcic infection available, would it be fair to have a control series composed of babies that had no prophylaxis at birth, by either a sample or an alternate case method, in order to determine the incidence of gonococcic ophthalmia?

Our experience with the silver nitrate reaction is the same as Dr. Sweet's. I think most health department officials fail to realize that this purulent reaction is so common that if state laws requiring submission of samples of all purulent discharges from the eyes were strictly carried out there would not be enough bacteriologists in the department to do the examinations. The time factor, therefore, enters into the picture; most of these reactions, interestingly enough, come on in four to eight hours after birth.

One of the characteristics of a silver nitrate reaction is that the lids are stuck together and when they are separated as much as 1 cc. of green, purulent material explodes out under pressure.

Use of silver nitrate is still required in our community. We have conducted some studies to see whether this reaction could be minimized. We thought the irritation responsible for the reaction might be due to the eye's not draining because the lids were sealed together. The simple procedure of coating the eyelid and eyelid line with 1 per cent yellow mercuric oxide ointment prevented the eyelids sticking together and cut down the incidence of this distressing reaction.

Dr. Katharine Dodd, Cincinnati: Was Dr. Sweet able to follow the babies well enough to tell whether the one injection of penicillin masked the symptoms of syphilis later on or interfered with the diagnosis of any other infection that might have been present in the first few days of life?

I should think it dangerous to give newborn babies one injection of penicillin because they might have septicemia with Treponema pallidum or some other organism. I should not like to use penicillin as prophylaxis against gonorrhea in our nursery, where we have both syphilis and occasional sepsis. The single injection might not be sufficient to cure the disease but might modify or delay the appearance of symptoms.

Dr. Edward B. Shaw, San Francisco: Some note should be made of the fact that very real damage is caused when silver nitrate solution is applied into

the nearly tearless eye of a newborn baby. In the original Crede prophylaxis, silver nitrate solution was first introduced and then the eye was promptly and thoroughly irrigated with isotonic sodium chloride solution; the sodium chloride arrested the irritating effect of the silver salt by precipitating insoluble silver chloride. I have long suspected that the irrigation with saline solution terminated not only the irritating effect but also the prophylactic action of the silver salt and, at the same time, contributed more to the prevention of ophthalmia than did the antiseptic action of the silver nitrate.

In many hospitals, the silver nitrate solution is conscientiously applied but subsequent irrigation is not faithfully employed. Severe chemical conjunctivitis then not infrequently occurs, and for several days thereafter pus will roll out when the lids are forced open. Secondary bacterial conjunctivitis is not infrequent. Actual damage, to be sure, is seldom severe but may persist a long time, especially if the child has congenitally small nasolacrimal ducts. This persistent inflammation not only is disturbing but causes the infant constantly to squint or to have actual difficulty in developing normal vision; it especially may interfere with the early development of ocular fusion.

Most ophthalmologists are of the opinion that historically this procedure has greatly reduced the incidence of ophthalmia neonatorum, and they are inclined to minimize the resultant damage. I submit, however, that such injury in the cause of prophylaxis is inconsistent with the actual risk of gonorrheal infection which, if it occurs, can be effectively and promptly treated with penicillin. In California only 13 such cases were reported in 1949, and previous years showed a steady diminution in their number. For the prevention of this small number of expected cases, thousands of California babies were subjected to the procedure.

I firmly believe that the Crede prophylaxis is completely indefensible in the light of present knowledge of the antibiotic treatment and prevention of newborn ophthalmia.

DR. ALTON GOLDBLOOM, Montreal, Canada: I should like to ask, first, whether there have been any penicillin reactions from this treatment.

DR. WILLIAM A. REILLY, Little Rock, Ark.: I should like to have Dr. Sweet comment on the relative value of the local instillation of penicillin, which we have used with some success, in order to answer partly Dr. Dodd's criticism.

DR. LEWIS K. SWEET, Washington, D. C.: The questions of Dr. Reilly and Dr. Clifford concerned the method of using penicillin locally. When I started this work, Dr. Clifford brought up this question: Can we do without prophylaxis altogether? I do not know. We are coming close to the legal limits when we do what we are doing now. The reason I am sure we have uncovered all the cases of gonococcic conjunctivitis occurring in our infants is that a few persons in our health department look somewhat askance on this experiment. They keep a close watch and inform me of every patient who is reported to have had gonococcic conjunctivitis and ask what kind of prophylaxis the infant had. I think if I tried to do without prophylaxis I would be stopped immediately. There may be places where that can be done, but it cannot be done in Washington at the moment.

The reason for not using local instillations of penicillin is that, in his early work, Franklin was giving three or four instillations. We do not have enough nurses for so many instillations. Franklin has since reduced the number to only one, and he has had good results. He has had no gonorrheal conjunctivitis in either the treated or the control groups; therefore, he does not know whether he is preventing gonococcic conjunctivitis or not. The same thing is true at the Johns Hopkins Hospital. I prefer intramuscular injections because I can have the syringe ready and can give the penicillin quickly and accurately; I know I get it in, and I know

what I have given the baby. Some of these patients who are born after difficult deliveries, particularly after a face presentation, are likely to have an edematous face. I do not believe any one can get anything into the conjunctiva of an infant born after a face presentation or with an edematous face from some other cause.

There is always a possibility that one might introduce an infection into the eye with the medication. Some of the conjunctivitis in our penicillin-treated infants may have resulted from the local use of boric acid solution. Therefore, it seems to me that if an effective antibiotic treatment is developed which we can use systemically, it will be almost the ideal situation, and it will not be a very big step to Dr. Clifford's ideal of treating the mothers and not the babies.

Dr. Goldbloom asked a question about reactions. We have seen no evidence of reaction. I cannot state that there have been none. I cannot be sure that, if these patients come back in six months to a year with pneumonia or meningitis, they will not be sensitive to penicillin. So far we have seen no evidence of sensitivity.

Dr. Dodd touched the one most vulnerable point in this whole program, and I cannot answer her question as yet except to say that, without making a careful statistical study, I have seen no evidence of any difference in our incidence of congenital syphilis. It is true that 10 per cent of the mothers have or have had syphilis. Fortunately, owing to the efforts of our Venereal Disease Bureau about 99 per cent of the syphilitic mothers have been treated during pregnancy, and the incidence of congenital syphilis is low. We watch the serologic reactions of infants born of syphilitic mothers closely, however, and at present we can detect no evidence of difficulty in the diagnosis of congenital syphilis that may be attributable to the intramuscular use of penicillin at birth.

I agree with Dr. Shaw that we can treat patients with gonorrheal conjunctivitis so easily now with penicillin or sulfonamides that the giving of instillations to the thousands of babies born in California every year to try to prevent one or two cases of gonococcic conjunctivitis is like straining at a gnat and swallowing a camel. However, in most states the law still requires us to strain at the gnat!

Studies on Absorption, Distribution and Excretion of Aureomycin, Chloramphenicol and Terramycin. Dr. Andrew D. Hunt Jr. (by invitation), Dr. Richard S. Kelly Jr. (by invitation), Dr. Coleman M. Whitlock Jr. (by invitation) and Sylvia G. Tashman (by invitation), Philadelphia.

Aureomycin was given to a number of infants and children orally in a dose of 5 mg. per pound (11 mg. per kilogram) of body weight. With the use of the turbidimetric method of assay, measurable amounts of the drug were detected in the serum within one hour, with peak levels being attained in two to four hours. The average peak serum level ranged from 1 to 2 micrograms per milliliter; six hours after injection the level began slowly to decrease, but eight hours after injection aureomycin was still present in the serum. Single oral doses of 10 mg. per pound (22 mg. per kilogram) of body weight did not produce significantly higher serum levels.

A cumulative effect was observed in some children who received continuous doses of 5 mg. per pound (11 mg. per kilogram) every four hours for several days. Definite diffusion into the spinal fluid occurred on such dosage. Rectal administration of similar amounts of aureomycin produced no detectable serum levels.

Intravenous administration of aureomycin, 3 mg. per pound (6.6 mg. per kilogram) of body weight, gave peak serum levels averaging 8 micrograms per milliliter,

with levels above 1 microgram per milliliter being sustained for eight to ten hours. These concentrations suggest diffusion of aureomycin to other than extracellular fluid in appreciable amounts.

Chloramphenicol, 5 mg. per pound (11 mg. per kilogram) of body weight, orally, produced insignificant serum levels. Ten milligrams per pound (22 mg. per kilogram) produced peak levels in one hour, averaging 10 micrograms per milliliter. Twenty milligrams per pound (44 mg. per kilogram) produced peak levels averaging 20 to 30 micrograms per milliliter of serum. Levels above 5 micrograms per milliliter were maintained at least eight hours on the last dosage. Rectal administration of chloramphenicol gave serum levels indicating absorption of approximately 50 per cent, compared with the oral route. Serum levels after intravenous administration of chloramphenicol were also presented.

A fundamental difference in the mechanism of absorption between the two antibiotics from the gastrointestinal tract was suggested.

From the data tentative conclusions on the absorption, distribution, excretion and dosage of the three antibiotics were presented.

Collections of Subdural Fluid Complicating Acute Bacterial Meningitis.

Dr. R. James McKay Jr. (by invitation), Dr. Russell A. Morissette (by invitation), Dr. John A. V. Davies, Dr. Franc D. Ingraham and Dr. Donald D. Matson (by invitation), Boston.

During the past year 17 patients were found to have collections of subdural fluid complicating acute bacterial meningitis. Remission of undesirable symptoms accompanied removal of the fluid, which had characteristics similar to those seen in chronic subdural hematoma of infants and children. Bilateral temporal burr holes were made on all patients, and subdural membranes were observed in nine instances. Review of clinical records revealed 12 more similar patients, seven of whom had subdural membranes. A review of 218 autopsy protocols of children who died of acute bacterial meningitis revealed 25 additional patients in whom significant collections of blood, pus or xanthochromic fluid were observed in the subdural space at postmortem examination. Only two of these had subdural membranes. The condition was found most frequently among patients with meningitis due to Hemophilus influenzae and Pneumococcus but was also observed in children with meningococcic and staphylococcic infections. Twenty of the 29 patients in whom diagnosis was made during life were under 1 year of age, and 13 of these had subdural membranes. The incidence of membrane formation was noted to be higher after the advent of specific antibacterial chemotherapy, but there was no relation to treatment with any one agent or to intrathecal therapy; neither trauma nor the degree of purulence of the cerebrospinal fluid could be implicated as an etiological factor.

DISCUSSION

Dr. Margaret H. D. Smith, New Orleans: We have been extremely interested in Dr. McKay's series of patients since last summer, when Dr. Blair Batson, of Vanderbilt University, Nashville, Tenn., pointed out to my associates and me that we were at opposite ends of the country making similar observations.

Just now I heard a number of persons gasp at Dr. McKay's figures; our patients with meningitis in the last 18 months show a similar incidence of subdural effusions. In that time we have observed 26 patients with subdural effusions. After the first 20 patients we tabulated our results and found that of a total of 43 children with meningitis, 20 had subdural effusions; so it is apparently true

that approximately one half of all the patients under the age of 1 year—or in our series under the age of 2 years—who acquire meningitis have subdural effusions.

In a number of patients effusions of fluid were present on both sides. In others the effusion was present on one side only. In most cases 5 to 15 cc. was the usual amount of fluid. In several patients, however, we were able to withdraw 60 cc. repeatedly.

If one tabulates the incidence of subdural effusions according to the day of disease—not the hospital day, but the day of the onset of illness, as well as one can determine it—the highest incidence seems to be between the seventh and the thirteenth day.

In three of our 26 cases bacteria could be cultured from the subdural fluid at the time of the initial tap, and in all three cases the organism was the same as that presumably responsible for the meningitis. I say "presumably responsible" because it has been our experience to admit a patient, who previously received treatment elsewhere, and find that the spinal fluid contains no organisms, while the subdural fluid, which is still infected, enables us to make a correct etiological diagnosis.

Our indications for subdural tap are exactly the same as Dr. McKay's, with one addition: In any patient who has received chemotherapy for meningitis before coming to the hospital subdural taps are performed routinely.

All our patients were treated by means of repeated subdural taps rather than by operation. We are not sure what the best mode of treatment is; however, we believe that the dura of all these patients should be tapped repeatedly until dry; then if their condition does not progress satisfactorily, the indications for operation should probably be the same as in the case of subdural hematoma.

Subdural effusions, often with infected membranes, are perhaps the reason for recurrent meningitis, in the same way that pleuropneumonia is often the background for recurrent septicemias lasting many months.

I might say that not only are we seeing subdural effusions in this country, but, according to a recent letter from Mr. A. N. Gutkelch, subdural effusions are being recognized frequently at the Royal Manchester Children's Hospital, in England.

Dr. R. James McKay, Boston: In the matter of unilateral or bilateral effusions, we, too, have found a number of patients with bilateral effusions. Interestingly enough, those patients with focal signs, either hemiparesis or focal convulsions, tended to have unilateral effusions on the opposite side. In all but one of our cases with infected fluid, we found the lumbar puncture fluid to be bacteriologically negative at the time the subdural tap was done.

So far as the time incidence of appearance of subdural fluid in meningitis is concerned, our experience agrees entirely with Dr. Smith's, as does the amount of fluid obtained. We have had one or two patients from whom we were able to get only 1 or 2 cc. of fluid at the time of tapping, but large amounts of serum-like fluid have drained for 24 to 30 hours following the tap through the needle puncture.

The matter of treatment, of course, needs further clarification. There is much disagreement throughout the country concerning the best treatment for chronic subdural hematoma of infants. It has been the policy at Children's Hospital, in Boston, to perform excision of the membranes, but at the same time we recognize that undoubtedly there are patients who would recover completely merely with repeated tapping.

Observations on the Role of Intestinal Flora in Growth and Disease. Dr. Paul Gyorgy and Dr. Joseph Stokes Jr., Philadelphia.

The role of the normal intestinal flora as a source of vitamin-like nutrients has long been recognized. Analysis of the etiological factors instrumental in the pro-

duction of experimental hepatic necrosis, as well as clinical observations on the beneficial effect of aureomycin in subacute or chronic hepatitis and in hepatic coma, led to the assumption that metabolites of the normal intestinal flora may injure the liver and may promote the development of hepatic necrosis. In rats fed a "necrogenic" experimental ration, the production of hepatic necrosis was prevented or significantly delayed by antibiotics (aureomycin, streptomycin) mixed with the diet. Aureomycin proved to be more effective than streptomycin. This result is in line with the well known fact that resistance to streptomycin develops in bacteria much easier and sooner than to aureomycin. It is assumed that both aureomycin and streptomycin exert their beneficial effect by suppression of intestinal bacteria, probably Escherichia coli and by the elimination of toxic metabolites of these bacteria. These metabolites appear to be injurious not only to the liver but to the general well-being of the animals. Rats receiving aureomycin or streptomycin in their basal necrogenic diet showed a better growth curve than animals fed the basal diet alone. Thus, "intestinal autointoxication," if it exists, may have a far reaching effect in growth and disease.

Experiments are contemplated jointly with Prof. Reyniers and his group at the University of Notre Dame, Ind., on the effect of a necrogenic basal diet in germ-free rats. It is postulated that hepatic necrosis will not occur in these animals.

Treatment of Disseminated Histoplasmosis with Ethyl Vanillate. Dr. Amos Christie, Dr. James G. Middleton (by invitation), Dr. J. Cyril Peterson (by invitation), and Dr. David L. McVickar (by invitation), Nashville, Tenn.

Until recently all reports in textbooks and in the literature seemed to indicate that the generalized disseminated infections with histoplasmosis are uniformly progressive and fatal.

Many drugs, including glucosulfone sodium (promin®), actidione, penicillin, streptomycin, aureomycin, chloramphenicol, sulfonamides, stilbamidine, iodides, arsphenamine, mercurials and antimony have been tried in adequate doses by us and others without effect. No treatment, until the present study was undertaken, has been capable of influencing the downhill course of the infection with Histoplasma capsulatum when it becomes disseminated and progressive.

In July 1948, Dr. Harry Lewis, of the Institute of Paper Chemistry, Appleton, Wis., called our attention to a fungicidal compound—the ethyl ester of vanillic acid. This compound had been developed as a by-product in the manufacture of paper pulp. Experimental work done for the armed forces showed it to have fungicidal properties for some of the fungi which produce spoilage of foodstuffs. Initial studies in our laboratory revealed the growth of H. capsulatum to be inhibited by ethyl vanillate in concentrations of 20 mg. per 100 cc. in plasma-fortified mediums incubated at 37 C. (98.6 F.).

A review of our two years' experience with this chemotherapeutic agent was given. The physiochemical properties of the substance were described. Further in vitro studies were reported on, as well as the quantitative method for determining the presence of the fungicidal agent in blood and tissue. Results of toxicity experiments in animals and toxic reactions in the human being were also reported.

We gave it as a 40 per cent solution in olive oil by gavage. We have attempted to give as much as 1.5 Gm. per kilogram of body weight per day in divided doses. This has maintained blood levels between 17 and 35 mg. for six to eight weeks.

The material has been used therapeutically in 12 patients with disseminated and progressive histoplasmosis at this writing. Five of these infants and children are still alive and well or improving. These results are more encouraging when we

consider that in two of our failures the children were moribund when treatment was instituted and died within a week. A third child had extensive colitis with ulceration and diarrhea to the extent that a satisfactory blood level of the drug could never be attained.

As with other infections, the unknown factors, such as virulence of the organism, dose of the drug and resistance of the host, must be important in determining the course of the disease. Likewise, as in other infections, earlier diagnosis and earlier institution of therapy will undoubtedly improve the prognosis in all cases.

Ethyl vanillate is the only effective therapeutic agent for disseminated and progressive histoplasmosis which we have had an opportunity to try up to the present. The margin between effective therapeutic levels and those which produce toxic manifestations is only about 25 to 30 per cent, a margin of safety too small for a desirable therapeutic agent. However, progressive disseminated histoplasmosis is an infection of such grave prognosis that one seems entirely justified in using any agent which offers some hope of therapeutic effectiveness and which does not regularly produce severe toxic manifestations.

DISCUSSION

DR. KATHARINE DODD, Cincinnati: When one practices pediatrics in the Mississippi River Valley, one cannot help being greatly interested in a form of therapy which may be effective in generalized histoplasmosis. In Cincinnati we see two or more patients with generalized histoplasmosis a year and at present can do nothing specific for them. As a matter of fact, from published work on the action of the antibiotics on yeasts and molds, one is led to believe that perhaps the use of antibiotics may be making the condition of these patients worse rather than better.

I think one should be cautious about making claims for any form of drug therapy in histoplasmosis, because the disease is an extremely variable one. Burnell and Furcolow reported 10 proved cases of histoplasmosis in 1948. Of these, two were of infants, one 5 months and one 20 months of age. Both had fever, splenomegaly, leukopenia, positive blood cultures and positive bone marrow cultures. In one granulomatous lesions were observed throughout the spleen which was removed at operation. The patients were ill from five to six months; yet both recovered without therapy. A third patient in their series was a 13 year old boy who probably had histoplasmosis only of the lungs. He also recovered without therapy. There were two older patients who had histoplasmosis confined mainly to the lungs. One patient, at the time of their report, was showing improvement without therapy and had gained about 18 pounds (8.2 Kg.); the condition of the other was going downhill.

We at Cincinnati have had one case of generalized histoplasmosis proved by culture of blood, marrow and liver and a liver biopsy which showed granulomatous lesions. The child recovered without therapy. In a second child, a baby about 5 months of age, histoplasmosis could not be proved. The baby had enlargement of the liver and spleen, anemia and leukopenia. The reaction to the histoplasmin test was positive. All cultures were negative; nevertheless, a biopsy of the liver showed granulomatous lesions similar to those seen in proved cases of histoplasmosis. The child had a prolonged prothrombin time and was ill because of bleeding. When the prothrombin time was brought to normal with vitamin K therapy, the baby began to do much better. We tried to send this patient to Dr. Christie because we believe, as his last statement indicated, that in a disease as serious as generalized histoplasmosis it is well worth trying a method of therapy which is apparently

not dangerous, even though it has not yet been proved to be beneficial. The parents, however, were unwilling to take the child to Nashville. At last report the baby is recovering without therapy.

Two other cases of histoplasmosis of the lungs have been reported from Columbus, Ohio. Both patients had enlarged spleens and positive blood cultures. These patients are now well without specific therapy. One other patient in Cincinnati, not at our hospital, was proved to have generalized histoplasmosis and is recovering without therapy.

If one believes that the majority of patients one sees in this region of the country with calcification throughout the lungs, and sometimes the spleen, liver and lymph nodes, and with positive histoplasmin and negative tuberculin reactions have cured histoplasmosis, there must be many persons with generalized histoplasmosis who recover without therapy.

I should like to ask Dr. Christie a question. Does his method test for ethyl vanillate in the blood or just for vanillic acid? Is he sure when he gives ethyl vanillate by mouth that it is absorbed as ethyl vanillate?

Dr. Clement A. Smith, Boston: I want to ask whether Dr. Christie can tell us anything from in vitro measurements about the effect on monilial infections.

Dr. Lyman T. Meiks, Indianapolis: At Indiana University Medical Center we have had seven instances of histoplasmosis with one spontaneous recovery. I have word of mouth information that many other cases have been seen to date with a fatal outcome. Therefore, I am impressed by the recovery of five patients of 12 with ethyl vanillate therapy, particularly when several of the patients were near death at the time the treatment was started.

Since there is some prospect of therapeutic effect from this substance, it seems that the need for early and accurate diagnosis is greatly increased. The current methods are ordinarily effective in establishing the diagnosis with certainty before death, but, unfortunately, the positive signs often do not appear until the patient is in a serious condition. Recently, we have been using a complement fixation test for all suspected patients, and in three instances that reaction has been positive before cultures or smears became positive. In each of these three cases the cultures subsequently yielded the organism. No false positive reactions have been obtained with the complement fixation test.

Perhaps it would be well to call attention to a clinical picture we have seen in four of seven patients. In addition to the anemia and enlarged spleen, we noted reticulocytosis (5 to 10 per cent), with a slight elevation of bilirubin (van den Bergh) and normal cell fragility. The bone marrow showed signs of erythropoietic overactivity at a time the parasites were not demonstrable.

We believe this particular combination may be highly suggestive of the condition, and its observation will lead us to be energetic in our efforts to diagnose the condition more positively.

Dr. Warren E. Wheeler, Columbus, Ohio: I should like to add my agreement to Dr. Dodd's note of caution that spontaneous remissions do occur in this disease. In addition to the two cases she cited, my colleagues and I subsequently had another, that of a child 3 years of age, who seems to be recovering.

My main comment may be uncharitable, but I am struck by the two groups of patients in this report. One was the group of patients who were sick for a long time, in whom treatment was started and continued for a long time and who eventually recovered. The other group of patients consisted of those who must have been sick for a long time to get to the sad state in which they were described and who then died suddenly after treatment was started.

I cannot help but be reminded of the parallelism between the latter patients and the patients with tetanus to whom tetanus antitoxin is administered intrathecally. Many such patients should be expected to live for several more days, but they suddenly die within 24 hours after the intrathecal treatment.

Perhaps this is not the case here, but I should like to inquire whether or not these patients who died after two, three or four days of treatment were really that moribund, and were they expected to die that soon after treatment was begun, or could this be a signal to be a little cautious of the immediate toxic effects of ethyl vanillate?

DR. AMOS CHRISTIE, Nashville, Tenn.: Dr. Dodd, Dr. Wheeler and Dr. Meiks brought out many of the points I should have liked to discuss but for the pressure of time.

It is unnecessary to remind me and my associates of the significance of the benign infections with H. capsulatum, which we described at this meeting several years ago and have been in the process of attempting to elucidate ever since in studies at Vanderbilt. The cases reported this morning are all, I assure you, cases of histoplasmosis which are to this infection what miliary tuberculosis is to tuberculosis, that is, disseminated and progressive.

I would much rather have presented a paper to show the extent, frequency and type of benign infections we are seeing now in children or infants, whose histoplasmin skin test reaction has converted from negative to positive, and in whom complement fixation antibodies have developed. We have seen on roentgenograms the remarkable pulmonary infiltrations, some of which have produced positive cultures. Then successive healing from infiltration to pulmonary calcification takes place.

I appreciate the interjection of the point of view that this is a variable disease much like tuberculosis, with primary infections and occasional dissemination taking place for reasons which we do not understand, such as the resistance of the host and the virulence of the organism.

In one of the abstracts in this meeting, Dr. Klingberg reports on 11 cases with one apparent recovery. This is, at least, another control series.

The material in the blood which we measure may not be ethyl vanillate; it may be vanillic acid; it may be some conjugate. I might say at this time that so far as vanillate is concerned we have measured levels in one baby of up to 50 mg. per 100 cc., and we have not been able to influence this systemic fungous infection at all. The same is true for some strains with in vitro experiments with vanillate.

As I attempted to imply, we are not too excited about this material. We recognize its toxic limitation, but we stumbled onto it in a period of desperation. Our staff members were profoundly impressed by what happened to the first baby I described. Then it seemed that we were duty-bound to discover how close this might be to the answer in the treatment of this serious infection, which, when it becomes disseminated and progressive, almost uniformly ends fatally.

Transformation of Type Specificity of Hemophilus Influenzae. DR. HATTIE E. ALEXANDER and GRACE LEIDY (by invitation), New York.

After the great discovery of Avery, MacLeod and McCarty (*J. Exper. Med.* **79**:137, 1944) that highly specific desoxyribonucleic acids direct the inherited characteristics of pneumococci, the cytochemists have made important contributions; they suggest that all cells are equipped with delicately balanced desoxyribonucleic acid systems which act as heritable units or genes.

The facts learned from the bacterial world suggest that when cells function abnormally as a result of mutation the character of their desoxyribonucleic acids differs from that of the parent cells and is responsible for their change in function. The far reaching implications of these statements in the fields of genetics, virus and cancer research rest basically on the proof that highly specific desoxyribonucleic acids of bacteria function as genes. Examination of the evidence for this proof formed the basis of this paper.

A large quantity of encapsulated cells of each of the six types of Hemophilus influenzae were processed by McCarty's latest method (*J. Exper. Med.* **83**:89, 1946) for isolating Pneumococcus desoxyribonucleic acid up to the point of elimination of specific polysaccharide, ribonucleic acid and somatic carbohydrate. These transforming principles were designated T_p with the letter of type of origin. The T_pb, or the T_p from type *b*, was further purified by McCarty's method and was labeled *DNAb;* the resultant product was free of specific polysaccharide and was shown to contain desoxyribonucleic acid by means of the diphenylamine reaction of Dische and the Stumpf reaction. Transformation was induced uniformly in concentrations as low as 0.01 microgram per cubic centimeter. The transforming activity was completely destroyed by a crystalline desoxyribonuclease.

Summary of Transformations of Hemophilus Influenzae

	Transforming Substance in Environment					
R Cells *	Tpa	DNAb	Tpc	Tpd	Tpe	Tpf
Ra	+	0	0	0	0	0
Rb	+	+	+	+	0	0
Rc	0	0	0	0	0	0
Rd	+	+	+	+	+	0
Re	0	0	0	0	0	0
Rf	0	0	0	0	0	0

* Letter refers to type from which R cells originated. For explanation of other abbreviations, see text.

The environmental factors necessary for activity of the H. influenzae-transforming principles appear to be identical with those essential for transformation of pneumococci by their desoxyribonucleic acids.

The table lists the results obtained with transforming principles of each of the six types of H. influenzae.

A number of questions are raised by the facts presented, only one of which can be answered now. Does the transformation by desoxyribonucleic acids explain the origin of bacterial species or play a role in the virulence of infection and thus promote epidemics? Can the nontypable nonpathogenic H. influenzae which inhabit the nasopharynx of the majority of children and adults during winter be transformed to type *b*? Proof has been offered that this change can be effected in vitro in a predictable uniform fashion by the genelike action of desoxyribonucleic acid isolated from type *b* H. influenzae, and, therefore, the studies suggest that transformation in the nasopharynx under suitable stimuli is a real possibility. But more important than these is the fact that demonstration of similar patterns of genetic control for members of two different bacterial families adds weight to the suggestion that the functions and structure of all cells are controlled by delicately balanced desoxyribonucleic acid systems and also to the possibility that abnormal functions of cells may be changed by altering these systems.

Compulsory Rooming-In at Duke Hospital. Dr. Angus McBryde (by invitation) and Dr. Wilburt C. Davison, Durham, N. C.

A compulsory rooming-in program was begun at Duke Hospital three years ago, not primarily for the psychological advantages, but in order to avoid the possibility of epidemics, especially of diarrhea of the newborn, in the nursery. A year was required to persuade the staff members that rooming-in was desirable, the greatest opposition naturally coming from nurses and obstetricians, although several of the pediatricians were hard to convince at first. For three years all possible white newborn infants have been bathed in the delivery room and placed in ordinary single bassinets and wheeled to the room or ward with the mother. The bassinet is kept at the mother's bedside day and night during her entire stay in the hospital, from two to 10 days, with an average of seven days, unless the infant is abnormal or the mother's condition is critical or she is infected. In this manner 90 per cent of nearly 2,000 infants have avoided nursery contact. Our service for white newborn babies is composed of 26 beds, of which 11 are in private rooms. Regardless of their location the babies were kept with the mothers. We found no increase in incidence of infection in infants in the wards as compared with those with their mothers in single rooms. No additional equipment was needed, as all the infant's supplies were kept on a tray at the bedside table. Infants were considered as rooming in only when they were kept in the nursery for less than 24 hours initially. If, for any reason, it was necessary to remove the infant from the mother's room after he had been placed there, the procedure was considered a failure. Maternal reasons which caused the infant to be placed in the nursery composed five sixths of the total, of which toxemia, maternal infection and cesarean section were the majority. The main infantile causes were excessive pharyngeal mucus, difficult labor and malformations. Among the entire group who roomed in only five infants were removed from the mother's room because of infection, three with nonspecific conjunctivitis, one with diarrhea and one with omphalitis. The incidence of infection was much lower than in the usual nursery. During the first 30 months of our program the infants were cared for by the personnel of the nursery for the newborn and the mothers by nurses from the obstetric service. For the past six months a combined pediatric-obstetric service has been used, with one nurse caring for four to six infants and mothers for each eight hour period. All infants were placed on a self-regulation schedule, and the mother was encouraged to nurse the baby when he cried. The incidence of breast feeding in babies discharged from our service has been greatly increased by this measure. The program has been almost universally accepted by the mothers, as well as the fathers and grandparents, all of whom are allowed to visit the infant as they wish. The mother has a decided increase in confidence and in her ability to care for the child. The father also becomes acquainted with the infant and his problems early in life and is, therefore, willing to share the responsibility. Now that most obstetric patients are in good health, we believe that normal newborn infants born of healthy mothers should room in.

DISCUSSION

Dr. Amos Christie, Nashville, Tenn.: I should like to congratulate Drs. McBryde and Davison on the accomplishment of this plan in a population which is a little different perhaps from that in New Haven or in the other centers where rooming-in has been accepted.

I have had the opportunity personally to evaluate this. I fought for five years with administrators and other department heads, to try to bring our own nurseries up to the high standards recommended by the Academy and Dr. Clifford. I thought perhaps I should scrap that plan and advocate rooming-in, so I went to

Durham to see it firsthand. Dr. Davison allowed me to go into three of these six bedrooms shown by Dr. McBryde in his diagram. There was no possible opportunity for the women in the rooms to know who I was or what I wanted. I asked them various questions, some leading and some indirect. I was really amazed and gratified at the almost uniform response of the mothers. In the larger rooms the women, mostly in the low cost classes, all liked it. I talked to several graduate students' wives in private rooms, and almost uniformly they did not like the rooming-in plan.

In one room with five other mothers and babies was a woman who had lost her baby. This woman was caring for the other mothers' babies. She thought the rooming-in plan was excellent. I thought if her attitude was possible in those circumstances the plan had a great deal of merit.

I should like to ask one question, which perhaps is an administrative one, that recurs frequently in our thinking about these programs and their projection in our own hospitals: Does this plan take more nursing time or less?

DR. STEWART H. CLIFFORD, Brookline, Mass.: Drs. McBryde and Davison have had an unusual experience in being able to observe the results of the overnight conversion of a conventional hospital nursery to a completely rooming-in service.

The evaluation of this system as a means of controlling infection is made difficult by the marked reduction in the incidence of epidemic diarrhea in recent years. Massachusetts had 19 epidemics in the 10 years preceding 1946. At this point statewide institutes on the care of the newborn were held. There has been no widespread adoption of the rooming-in system, and for the last three years we have not had a single epidemic of diarrhea of the newborn in the state.

I am a greater believer in the rooming-in system when the mother desires it—I must admit I am bothered about the "compulsory" angle. I had hoped that before now some authority on mental hygiene would have commented on the "compulsion" aspect. It is my understanding that when there is a deep-seated aversion to such a procedure as breast feeding it may be harmful to use compulsion.

DR. ANGUS MCBRYDE, Durham, N. C.: The mothers whom we sent home during the first 24 hours were largely Negro mothers who were of a very low economic level, as a rule, since most of the Negro obstetric patients go to another hospital. They do well at home because their mothers, sisters and aunts usually had their babies at home. They do not object to going home after the first 24 hours. In addition, we have a good nursing service through the City Health Department, which allows a visit to each mother as needed during the first week at home. In this Negro group, I think, the incidence of breast feeding, because of the racial factor, is higher than in the other groups.

Dr. Christie and Dr. Clifford commented on the question of the intelligence level of the mother in relation to her liking of the rooming-in method, also on the question of compulsion. The mothers we have had the greatest difficulty with have been the wives of medical students, doctors and faculty members, and we have a great number of them. I hardly know how to comment on them. If a sympathetic obstetrician has explained the routine to them in advance, most of these mothers have absolutely no objection and prefer this method, although they have had one or two babies in the nursery in previous deliveries. The primipara usually likes rooming-in.

We have occasional women who have not grown up, who are not emotionally mature and have been pampered and who feel that having the infant in the room is an imposition. Our idea is that these women are adults and they should accept the responsibility for the child. We ought to be able to make them accept it. I think Dr. Clifford would hesitate to care for a child if his mother refused to let

him have the diphtheria toxoid injections and the other usual immunizations he should have. He does not ask her about that—he tells her. That is what we are trying to do with rooming-in, because we are convinced it is the answer to the nursery problem in our area.

The other problem is the matter of the education of our obstetrical colleagues. I am sure that in conservative Boston and other areas there is much more resistance to change than we have, as our services are so arranged that heads of the obstetric and pediatric departments may decide policy. This cannot be easily done in a private service where there are many attending physicians.

I think Dr. Clifford is entirely right about the question of epidemic diarrhea. We do not know that we have the answer, but by spreading the babies out in this manner and, as far as possible, allowing them to contact only those organisms that they will contact within a few days in their own environment, we feel we are lessening the chance for the various types of infection. We have had occasional thrush and impetigo, but nothing more than that, and none of these infections was severe enough to require special therapy.

The Pediatrician's Role in the Management of Personality Problems of the Adolescent. DR. WILLIAM A. SCHONFELD (by invitation), New York.

The pediatrician and the psychiatrist should work in close harmony to study the interplay of psychologic, organic and growth factors which during the second decade of life have such a profound effect on personality development. The family pediatrician is in a position, through his continued contact with the child, his parents and siblings, not only to contribute to the solution of problems which arise during the adolescent period, but also to guide and direct the growing child and his parents so that many of the so-called problems of adolescence may be prevented or at least minimized. The pediatrician and the pediatric psychiatrist must accept the responsibility of the management of the personality and psychosomatic problems of adolescence with the goal of preventive psychiatry.

The problems of growth and development, the need for adjustment to variations in this development and the indications for appropriate hormone therapy were discussed in detail. Sex education is more than the giving of anatomic and physiological data, it includes the broad concept of education concerning the role of the boy and the girl in their relationship to each other, the family and the community.

It is as wrong to look at all the difficulties arising in adolescence as phases in development which the child will outgrow as it is to make an issue out of every variant in normal behavior. Some of the symptoms which, if excessive, merit attention, investigation and psychotherapy are as follows: 1. Hostility and hatred directed toward the parents, siblings, schoolmates or members of a sex. Unresolved hostility is one of the most destructive of psychodynamic forces and may affect future social adaptation. 2. Shyness and preoccupation with a solitary occupation. This may indicate the child's inability to accept the comradeship of children of his own age. 3. Regression to infantile trends, e. g., enuresis, temper tantrums and vomiting. 4. Deviations in behavior of an antisocial character, such as running away from home, truancy, stealing, lying and other manifestations of defiance of custom or authority. Too often these deviations are looked on as merely a phase without significance, when actually they may be an expression of serious underlying emotional difficulties. 5. A sudden or gradual loss of interest in activities formerly of interest, academic work, athletics or hobbies. 6. A feeling of inadequacy in everyday affairs. 7. Repeated minor physical illness or greater than ordinary concern with physical health and development. 8. Guilt feelings. Although at times difficult to evaluate and understand, these may have a profound, destructive effect

on personality development. 9. Failure at school. The importance of intellectual status is usually relative to what is expected of the person and what he expects of himself, although success in school requires a basic level of intelligence and specific abilities. Frequently, a poorly adjusted program which does not consider the adolescent's interests, abilities and limitations may be the sole cause of the failure.

The psychodynamics behind these symptoms were discussed in detail, as well as the roles of the pediatrician and psychiatrist in their treatment. Treatment should be primarily concerned with the general adjustment of the child rather than with merely the elimination of presenting symptoms. Symptomatic treatment is no more effective in the management of personality difficulties than it is in the treatment of physical illness. One must look for the cause in unsatisfied needs. Psychotherapy does not always necessitate extensive and prolonged analysis. Frequently the problem is a superficial one responsive to more superficial technics.

Abdominal Pain as a Manifestation of Epilepsy in Children. Dr. Samuel Livingston (by invitation) and Dr. Francis E. Schwentker, Baltimore.

This report deals with clinical and electroencephalographic studies on 29 children who suffered with recurrent attacks of abdominal pain unexplained by organic lesions of the gastrointestinal or genitourinary systems. Psychiatric investigations were carried out in the majority of these patients.

In 14 patients the abdominal pain was followed by postictal-like exhaustion and sleep; in 15 patients the pain was not accompanied with sleep. Frank convulsions were present in none of the patients at the time they were first observed by us.

Electroencephalograms were done on each patient. In one specific instance an electroencephalographic tracing was obtained on a patient while he was having a paroxysmal attack of abdominal pain.

Of the 14 patients who had abdominal pain followed by sleep, 10 had abnormal brain wave patterns consistent with epilepsy. One of these patients presented a serious generalized cerebral dysrhythmia at the time he was having an attack of abdominal pain. To our knowledge, this is the only reported case with serial electroencephalograms demonstrating cerebral dysrhythmia occurring concomitantly with an attack of abdominal pain.

All the 15 patients who had abdominal pain unaccompanied with sleep had normal electroencephalograms.

Of the 14 patients with abdominal pain followed by sleep, 5 later had generalized convulsions. None of the 15 patients with abdominal pain unassociated with sleep has as yet shown convulsions. All 29 patients are being treated with diphenylhydantoin (dilantin®) sodium. Of the 14 patients with abdominal pain followed by sleep, 11 have been definitely benefited. None of the 15 patients with pain alone was favorably affected.

The results of this study suggested that the syndrome of recurrent attacks of abdominal pain followed by postictal-like exhaustion and sleep, together with electroencephalographic evidence of cerebral dysrhythmia, is a manifestation of epilepsy, or so-called abdominal epilepsy.

DISCUSSION

Dr. Alex J. Steigman, Louisville, Ky.: May I ask Dr. Livingston two brief questions? First, in some clinics pentylenetetrazole (metrazol®) is used in order to mimic the focal convulsions and reproduce the seizural pattern. I am wondering whether you have had any experience with the use of pentylenetetrazole in reproducing this abdominal picture?

Second, has there been an opportunity to study the siblings of any of these patients from the electroencephalographic standpoint?

DR. SAMUEL LIVINGSTON, Baltimore: We did not use pentylenetetrazole in this particular group of patients, although we have used it extensively in other patients. In our clinic we administer pentylenetetrazole only to those patients with epilepsy who are considered candidates for surgical intervention. The drug is given as a means of activation of cerebral electric response to those patients who have definite clinical epilepsy with either normal brain wave patterns or generalized cerebral dysrhythmias.

We did not study the siblings of the group of patients presented today.

During the past two weeks we had the opportunity to see two additional patients with recurrent attacks of abdominal pain. In each instance the abdominal pain was followed by prolonged sleep and exhaustion. One of these patients, a boy 10 years old, had had recurrent attacks of abdominal pain for some time. He was first seen in another hospital and was operated on for "appendicitis," and the appendix was found to be normal. He was referred to us at a later date, and when studied completely was found to present the entity described by us today.

I feel that it would be worth while to investigate the possibility of "abdominal epilepsy" in the many patients who have recurrent attacks of abdominal pain and who are operated on with negative findings.

Suppression of Androgen Secretion in Congenital Adrenal Hyperplasia. DR. LAWSON WILKINS, DR. ROGER A. LEWIS (by invitation), DR. ROBERT KLEIN (by invitation), and DR. EUGENIA ROSEMBERG (by invitation), Baltimore.

In congenital adrenal hyperplasia the major clinical manifestations are due to the excessive secretion of androgens. Previous attempts have been made to suppress the androgen secretion in cases of congenital adrenal hyperplasia by the administration of biologically inert steroids which resembled androgen in chemical structure. These attempts were unsuccessful. Cortisone has been given to three patients with this disorder in the hope that if given in quantities sufficient for or greater than the normal needs of the body it might suppress the endogenous activity of the adrenal glands, including the hypersecretion of androgen. The first patient was treated with 100 mg. daily, the second with 50 mg. daily and the third with 25 mg. daily.

In all three cases the excretion of 17-ketosteroids was reduced from levels of 30 to 60 mg. per day to 4 to 6 mg. per day. The rapidity of the drop varied from three to ten days according to the dosage. The suppressive effect on the ketosteroid excretion was maintained throughout treatment, which in one case was continued as long as 45 days. On discontinuance of treatment the urinary 17-ketosteroids did not rise until after 10 to 12 days. The urinary estroids followed the same pattern. The urinary neutral reducing lipids were sharply decreased but rose again after 10 days of treatment because of the excretion in this fraction of a portion of the cortisone administered.

With the doses of cortisone given, changes in the nitrogen, carbohydrate and electrolyte metabolism were not apparent. The eosinophil counts fell slightly in two cases.

In the patient who was treated with 25 mg. of cortisone daily, an intercurrent infection caused a temporary rise in all types of urinary steroids, indicating that the adrenal gland was still capable of responding to an increased adrenocorticotropic stimulus due to stress. On the thirty-eighth day of treatment the administration of 80 mg. of ACTH produced a minimal response with a slight rise in urinary steroids.

Studies are in progress to determine whether continued treatment with cortisone causes a progressive decrease in the responsiveness of the adrenal gland to stress.

During the short periods of treatment studied no clinical changes in virilization could be observed. It is planned to carry out long periods of treatment to determine whether the androgenic activity of the adrenal gland can be suppressed indefinitely and whether cortisone will arrest the progressive virilization in these patients.

DISCUSSION

DR. ANDREW D. HUNT JR., Philadelphia: I should like to ask Dr. Wilkins what he feels the role of cortisone would be in a patient with the adrenogenital syndrome with concomitant adrenal insufficiency if such a patient were being maintained with desoxycorticosterone acetate. Would cortisone produce an antagonistic action to desoxycorticosterone acetate? Or is it possible that cortisone therapy alone might maintain such a patient?

DR. LAWSON WILKINS, Baltimore: I cannot answer your question as yet; I hope to within a month or two. I am glad you brought out the point that there are a number of groups of patients with various manifestations of congenital adrenal hyperplasia. In some there is no evidence of any manifest disturbance in the electrolyte control; in others there is a potential or an active deficiency in the electrolyte control that may lead to the addisonian complex. The patients in the latter group frequently require the administration of desoxycorticosterone and an increased salt intake for maintenance.

I am anxious to study this type of patient. It is quite possible that the salt-losing patient may be made to lose salt more rapidly with cortisone and may need a greater requirement of desoxycorticosterone to balance it. I think such a case will have to be studied carefully.

There might be some danger of throwing a patient of this sort into an acute adrenal crisis, and one will have to learn how to balance the two hormones exactly. We have such a patient at present who is being given pellets of desoxycorticosterone and who is coming to us in two or three weeks for further study with cortisone.

Preliminary Observations on the Effects of Cortisone in the Treatment of Acute Rheumatic Carditis. DR. T. N. HARRIS (by invitation), DR. WILLIAM B. ABRAMS (by invitation), DR. THOMAS F. P. LEO (by invitation) and DR. JOHN P. HUBBARD, Philadelphia.

Four patients with severe acute rheumatic carditis were treated with cortisone for an average of three weeks. Within the first few days of such treatment, there was clinical evidence of spread or exacerbation of the injection in some of these patients. Thereafter they proceeded to show improvement at a rate which may have been more rapid than that in average patients with disease of this severity given symptomatic treatment. Treatment with the drug was discontinued while the daily dose was approximately 0.75 mg. per pound (0.5 Kg.) of body weight. At that time, the erythrocyte sedimentation rates had become essentially normal and the cardiac signs had ceased to show change, although the rheumatic process in these patients was not considered quiescent. Within a few days after cessation of cortisone therapy, each of the four patients showed an exacerbation or return of clinical signs of active rheumatic fever, in each case within the clinical pattern of that patient on his admission for that episode.

On reinstitution of cortisone therapy in three of these patients, however, a rapid rate of clinical improvement was observed, especially in terms of well-being

of the patient and fall in the sedimentation rate, temperature, pulse rate and respiration rate within one week. Cardiac signs improved hardly at all during the first and second courses of treatment.

Effect of Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatic Fever. Dr. Albert Dorfman (by invitation), Dr. Delbert M. Bergenstal (by invitation), Dr. Earl P. Benditt (by invitation) and Dr. Frances E. Moses (by invitation), Chicago.

The discovery by Hench and Kendall and their co-workers of the striking effect of cortisone on rheumatoid arthritis has stimulated a large number of investigations on the role of the adrenal glands in a wide variety of diseases. It is already apparent that cortisone and ACTH have a definitely beneficial effect in a number of syndromes, including rheumatic fever.

In order to assess the effect of ACTH in rheumatic fever, a selected number of patients with long-standing active rheumatic fever were studied in great detail. These investigations included clinical observations, complete metabolic tests and studies of the nonspecific hyaluronidase inhibitor of serum.

ACTH shows a striking clinical effect on the disease process, including a reduction in pulse rate, temperature and sedimentation rate. Changes in cardiac status were shown by diminution of heart size and changes in murmurs. These observations were associated with maintenance of therapy, and all evidence of disease activity returned with cessation of therapy.

Toxic symptoms consisted of severe acne, rounding of the facies, retention of sodium, chloride and water and pronounced nitrogen loss. Little disturbance in carbohydrate metabolism was noted.

A striking decrease in the nonspecific hyaluronidase inhibitor was noted to parallel clinical improvement. The changes in inhibitor were similar to those previously observed to occur in spontaneous clinical improvement.

These data, together with the results of experimental studies presented, suggest that ACTH (through stimulation of the secretion of active adrenal hormones) may bring about changes in connective tissue which prevent the development of destructive lesions of rheumatic fever. Thus, the results obtained suggest that ACTH does not permanently alter the course of rheumatic fever but suppresses the manifestations of the disease, including myocarditis.

DISCUSSION

Dr. Henry Barnett, New York: It appears that the most striking difference between the experiences described by Dr. Dorfman and those of Dr. Wilson, as reported by Dr. Helper yesterday, is related to the duration of treatment required to obtain the effects observed. I think it would be of interest to hear from Dr. Wilson the reason she thinks the effects were observed after a much shorter period of treatment in the patients Dr. Helper reported on.

Dr. May G. Wilson, New York: I was interested in Dr. Dorfman's results. We did not have the courage to start ACTH therapy in patients who had been ill a long time. It seemed to us, from our experience, that if ACTH were given in adequate doses (and our doses were much larger) as soon as possible after onset of the disease, if ACTH is really effective, the course of the disease should be interrupted or terminated.

We did not expect the good result we obtained. After successful treatment of three patients, we were still doubtful. Studies on six or 10 patients seem required before the efficacy of ACTH therapy can be evaluated.

When ACTH administration was stopped after four days in a severely ill boy for experimental purposes, there was a recurrence within 24 hours which was less severe. Reinstitution of therapy after six days resulted in a termination of the rheumatic process. In another patient who was treated on the ninth day of illness, there was a good recovery, but on the sixth day after discontinuation of treatment with ACTH he exhibited a rise in temperature for five days without any other symptoms. It would appear that the acute exudative process is terminated but that the proliferative phase is not influenced by ACTH therapy.

DR. LAWSON WILKINS, Baltimore: I should like to ask Dr. Dorfman whether the persons who had cardiac failure were the ones retaining salt.

DR. ALBERT DORFMAN, Chicago: Yes.

Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in Children with Nephrosis. DR. SAMUEL SPECTOR and DR. LEROY W. MATTHEWS (by invitation), Cleveland.

Five patients with the nephrotic syndrome have been tested with ACTH. Three have shown a good response with complete diuresis. Two of these have further exhibited a striking reduction in albuminuria. The dosage employed has approximated 50 mg. (Armour) ACTH per day for one week, with subsequent gradual reduction of the dose over a three to eight day period.

The first patient, a 5 year old white boy, had manifestations of nephrosis for three years prior to therapy. He received ACTH for a 10-day period. Initially there occurred (1) a definite drop in eosinophils, (2) an increase in the albuminuria (from 2 to 4.8 Gm. per 24 hours), (3) a slight fall in urinary excretion of sodium and chloride and (4) pronounced transient fall in blood cholesterol. On the sixth day of therapy a marked reduction in albuminuria was observed, with eventual fall from 4.8 to 0.04 Gm. per 24 hours. Diuresis did not start until the seventh day and was maximum on the eighth day. During the four-day period of diuresis this 25 Kg. child lost 4 Kg. in weight. While in diuresis, his 24-hour urinary cortin excretin, as determined by Dr. Ralph Dorfman, was 5.0 mg., a fifteenfold increase, and his urinary 24-hour 17-ketosteroid excretion 13.6 mg., a sixfold increase over his pretherapy levels. Simultaneous elevation of the ratios of uric acid to creatinine and of creatine to creatinine was observed. With the onset of diuresis, a rapid rise in serum albumin, from 1.9 to 3.5 Gm. per 100 cc., and a fall in blood cholesterol, from 500 to 180 mg. per 100 cc., occurred in five days. During therapy there were no untoward symptoms and no glycosuria. The child has now been followed seven months and has remained free of edema and ascites. His blood pressure, which was formerly elevated, is 100/60. His 24-hour urinary albumin output varies between 0.3 and 0.5 Gm. His blood chemical values and sedimentation rate remain normal.

A second patient, a 3 year old white boy who had nephrotic manifestations for 16 months, showed a similar response during 14 days of ACTH therapy. On the fifth day of therapy his urinary albumin dropped from 2.0 to 0.7 Gm. per 24 hours and six days after therapy to 0.37 Gm. per 24 hours. His diuresis started on the eighth day and was complete three days after cessation of treatment.

A third patient, a 3½ year old white girl with nephrotic manifestations of 14 months' duration, had complete diuresis, beginning on the last two days of therapy, but without decrease in albuminuria.

Two patients have not had diuresis with ACTH therapy. One of these was inadequately treated, as evidenced by the lack of an increase in cortin or 17-ketosteroid excretion. The second patient, a 3 year old white girl with nephrotic

manifestations, azotemia and hypertension of seven months' duration, was first treated with cortisone without effect. With ACTH therapy, she showed no diuresis and no decrease in albuminuria but azotemia dropped; the nonprotein level fell from 75 mg. per 100 cc. before treatment to 48 mg. per 100 cc. after treatment. A second patient treated with cortisone also showed no response.

The response in the first two patients raised the question whether spontaneous remissions or those following measles might not also represent a response to stress with increased endogenous output of ACTH. The evidence obtained from studies on a 14 year old white girl who had diuresis with remission while receiving salicylates, which may or may not have influenced her recovery, would seem to suggest this. During her diuresis a fall in eosinophils from 380 to 180 per cubic millimeter, an increase in the ratio of uric acid to creatinine and an increase in 24-hour urinary 17-ketosteroid excretion from 4.8 to 10.8 mg. and in cortins from 0.08 to 0.32 mg. were observed. In her case a great decrease in urinary albumin appeared before the onset of the diuresis, with a rapid drop to normal levels.

The apparent failure of cortisone therapy, as compared with ACTH therapy, was further checked, with the assistance of Dr. Walter Heymann, in rats with nephrotic-like syndrome produced by the injection of nephrotoxic rabbit serum. In 16 such rats given cortisone, only slight or transient reduction in albuminuria was observed. In 9 rats given ACTH, one complete and one partial remission occurred.

Book Reviews

Antibiotics Derived from Bacillus Polymyxa. By P. H. Bell and others. Annals of the New York Academy of Sciences, volume 51, article 5. Price, $2.25. Pp. 160, with charts and tables. New York Academy of Sciences, American Museum of Natural History, Central Park W. and 77th St., New York 24, 1949.

This is a group of papers presented at a conference held by the Section of Biology of the New York Academy of Sciences. Groups of workers from several laboratories in this country and in England reported at about the same time the finding of an antibiotic substance from Bacillus polymyxa.

The name "polymyxin" was given to the substance by the American workers, whereas the English group called their substance "aerosporin," having obtained it from Bacillus aerosporus, which some consider the synonym of B. polymyxa. The antibiotic properties reported for these substances were similar, as were the organisms which produced the substances. Materials were exchanged between the laboratories to determine the relation of "polymyxin" to "aerosporin." The papers show that the main active components of "polymyxin" and "aerosporin" are not identical. They are closely related chemically and practically indistinguishable biologically. Other active substances are obtained from B. polymyxa. There is a common pattern of chemical constitution. The substances have a selective action for gram-negative organisms.

The papers cover the isolation, production, chemical characteristics and pharmacologic aspects of "polymyxin" and the multiplicity of antibiotic substances produced by B. polymyxa. Several papers compare the biologic activities of "polymyxin" and "aerosporin."

Most of the studies were carried out with experimental animals, mice, rats and dogs. "Polymyxin" and "aerosporin" have been used in a small number of cases of whooping cough, brucellosis, typhoid and gastroenteritis. The results were good in the instances of whooping cough and brucellosis and in some of the cases of gastroenteritis. The chief complication occurring in the course of therapy was renal toxicity, manifested by albuminuria, cellular casts, fixation of specific gravity and azotemia. These usually cleared up with cessation of medication. Anorexia, nausea, epigastric distress and drug fever occurred in a few of the patients. It is felt that the renal symptoms will be avoided by further purification of the drug.

The results obtained in the small number of cases reported should encourage further use of the drug in treatment of whooping cough and brucellosis and in those cases of gastroenteritis caused by gram-negative organisms.

Haemolytic Disease of the Newborn. By M. M. Pickles, D.M. Price, $4.50. Pp. 181, with 21 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

This book is a monograph on hemolytic disease of the newborn based on 116 affected children of 73 families from the Radcliffe Infirmary in Oxford, England. The historical evolution of the disease is given in considerable detail, and the author has set down most of the steps that went toward the final analysis of this condition. The antigens, immunization, pattern of disease and treatment are discussed in detail. The pathology is illustrated with examples from the author's own cases. The final chapter is devoted to the sequelae and other manifestations of the disease. An appendix deals rather fully with the actual serologic technics involved. The literature concerning this condition has been well reviewed, and a fair analytic study has been made of the accepted procedures.

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1. *Roth, B. B., Rohr, J. R., and Colwell, A. R.: Proc. House Staff Dept. Med., Wesley Memorial Hospital, Chicago, Ill. Feb. 6, 1940.*

2. *Rohr, J. H., and Colwell, A. R., Proc. Amer. Diabetes Assn. 5:37, 1945.*

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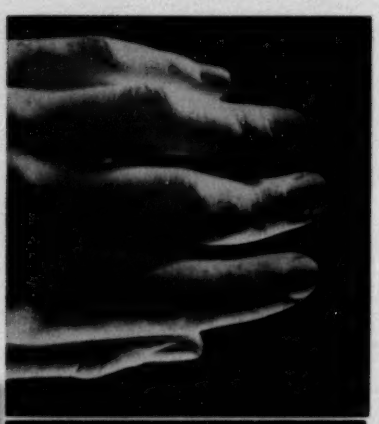

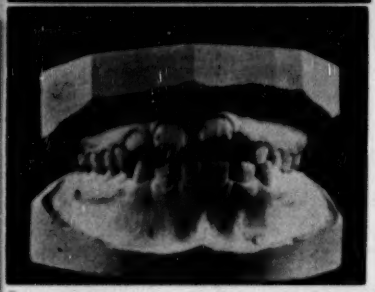

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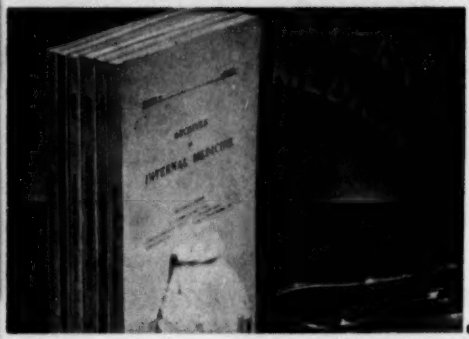

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*BIBLIOGRAPHY

Davison, F. W. — Acute Laryngotracheobronchitis. Archives of Otolaryngology. 47:455-464, April 1948.

Orton, H. B. — Acute Laryngotracheobronchitis. Archives of Otolaryngology. 33:926-960, June 1941.

Mitchell-Nelson—Textbook of Pediatrics. Fourth Edition. Pg. 747.

Morrison, William W., M.D. — Diseases of the Ear, Nose and Throat. Pg. 666, Diseases of Trachea and Bronchi. 1948.

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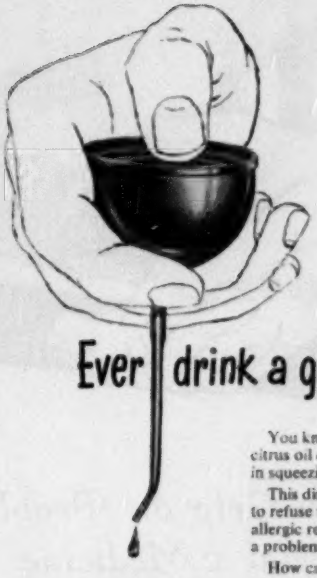

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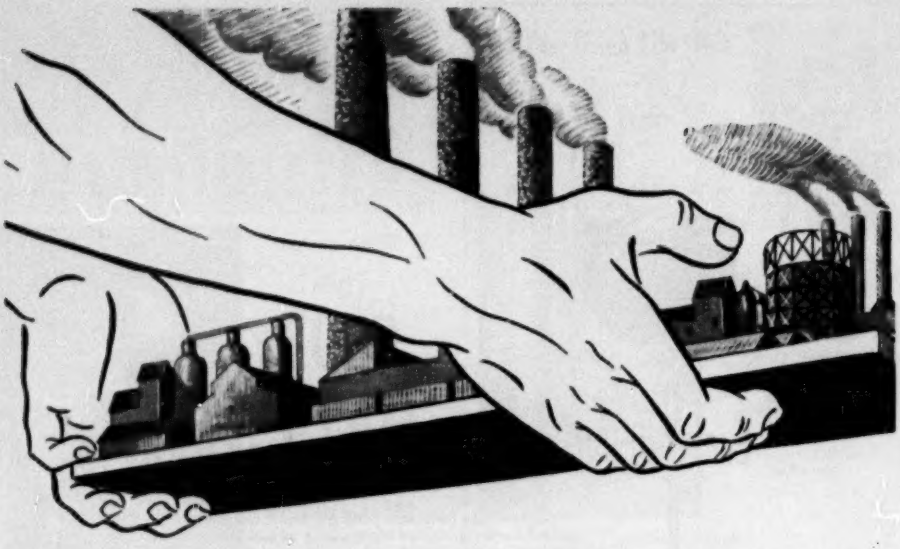

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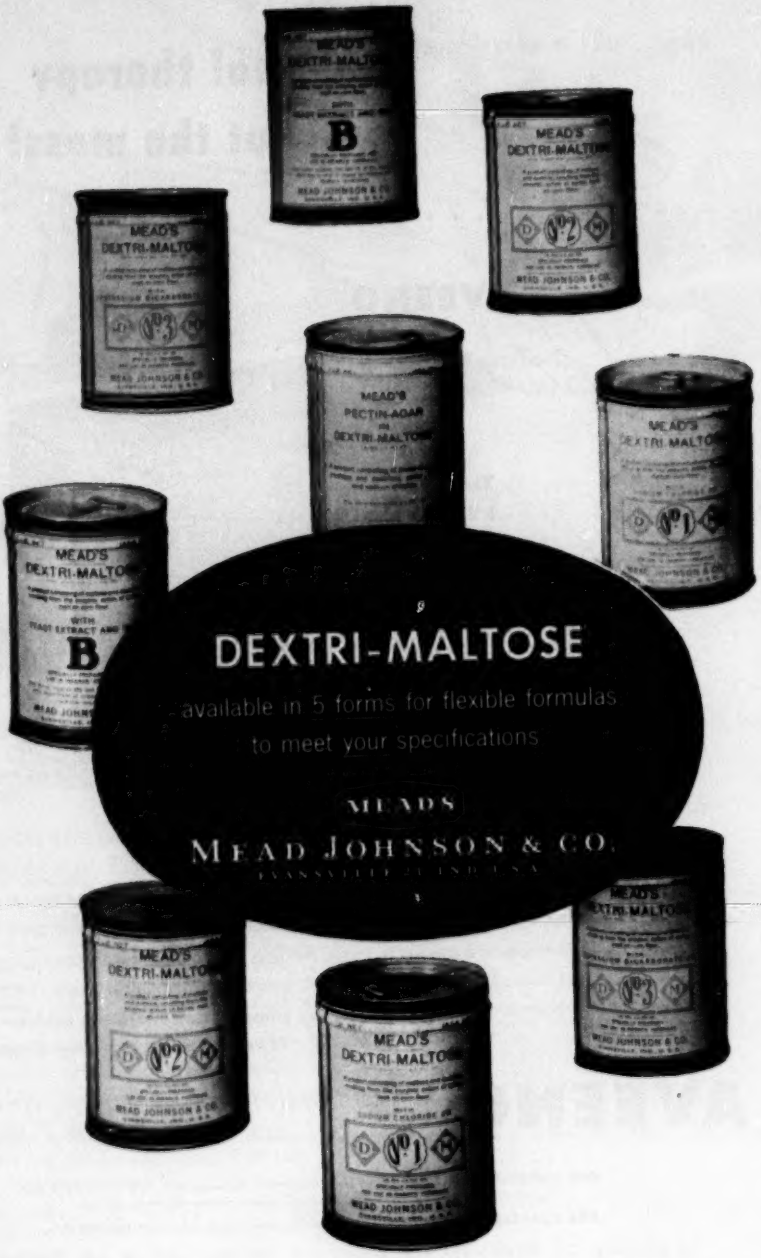
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1. Lennox, W. G. (1947), J. Amer. Med. Assn., 134:138, May 10.
2. Davis, J. P., and Lennox, W. G. (1949), J. Ped., 34:273, March.

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